Structural Brain Imaging Evidence for Multiple Pathological Processes at Different Stages of Brain Development in Schizophrenia

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The underlying neurobiology of emerging psychotic disorders is not well understood. While there is evidence from structural imaging and other studies supporting the popular notion that schizophrenia arises as a consequence of an "early neurodevelopmental" lesion, more recent findings challenge this notion. Evidence, including our own data, suggests that dynamic brain changes occur during the earliest stages of a psychotic illness, including around the time of transition to illness. In this article we review the available longitudinal and relevant cross-sectional structural neuroimaging studies focusing on both the very early neurodevelopmental markers (pre- or perinatal origin) and the later markers (late neurodevelopmental) around the period of transition to illness. Based on our review of recent findings, we suggest that the onset of psychosis is a time of active brain changes, wherein, for a proportion of individuals, (i) an early (pre- and perinatal) neurodevelopmental lesion renders the brain vulnerable to anomalous late (particularly postpubertal) neurodevelopmental processes, as indicated by evidence for accelerated loss of gray matter and aberrant connectivity particularly in prefrontal regions; and (ii) these anomalous neurodevelopmental processes interact with other causative factors associated with the onset of psychosis (e.g., substance use, stress, and dysregulation of the hypothalamic-pituitary-adrenal axis function), which together have neuroprogressive sequelae involving medial temporal and orbital prefrontal regions, as suggested by imaging studies around transition to active illness.

However, the pathological processes underlying such progressive changes during "late neurodevelopment" remain unclear but may reflect anomalies of synaptic plasticity, abnormal brain maturation, the adverse effects of stress, or other environmental factors. In this context, the features of schizophrenia, including the neuropsychological deficits and behavioral manifestations, can be understood as direct effects of these multiple pathological processes at various neurodevelopmental stages, including genetic and non-genetic etiological factors.

Key words: schizophrenia/longitudinal/neurodevelopment/neurodegeneration/brain changes/psychosis/prodrome/cognition/neuroimaging/stress/HPA axis

Introduction

It is now generally accepted that schizophrenia is associated with structural brain abnormalities, with the most consistent findings being enlarged lateral ventricles and reduced medial temporal and prefrontal lobe volumes.1–3 While such abnormalities are likely to be subtle,4 the nature, timing, and course of the associated neurobiological changes have proven difficult to elucidate.5–6 The dominant "neurodevelopmental" paradigm, positing that these structural brain changes are caused by early prenatal or perinatal nonprogressive insults,7–11 has been supported by longitudinal magnetic resonance imaging (MRI) studies that have found no progressive structural brain changes in advanced stages of illness (see below and table 1). This model has however come under increased scrutiny in light of more recent longitudinal MRI studies that have found progressive structural brain changes in advanced stages of illness (see below and table 1). This model has however come under increased scrutiny in light of more recent longitudinal MRI studies that have found progressive structural brain changes occurring from the earliest phases of the illness.12–18 The nature of the pathological processes underlying these progressive changes remains unclear but may reflect anomalies of synaptic plasticity, abnormal brain maturation, the adverse effects of stress, or other environmental factors (discussed below).

In this article we review the longitudinal and relevant cross-sectional imaging studies in schizophrenia and early psychosis and provide a detailed summary of relevant work from our groups. The evidence suggests that,
### Table 1. Summary of Recent Longitudinal Structural Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) Studies on Psychosis and Schizophrenia (partly derived from Weinberger & McClure80)

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Subject Groups</th>
<th>Average Age of First Scan (years)</th>
<th>Average Years of Follow-up</th>
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<th>Methods of Analysis</th>
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<th>Corresponding % Changes/Year in Controls</th>
<th>Brain Regions Showing No Change</th>
<th>Correlations Among Brain Changes, and With Other Clinical Variables</th>
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<tbody>
<tr>
<td>Degreuf et al., 1991</td>
<td>13 FES 8 Ctrlsl</td>
<td>not available not available</td>
<td>1</td>
<td>3.1 mm</td>
<td>manual tracing</td>
<td>none</td>
<td>total cortex</td>
<td>total ventricles</td>
<td>correlations were not found</td>
</tr>
<tr>
<td>DeLisi et al., 1992; 1995; 1997; 1998</td>
<td>50 FES/33 Ctrlsl 20 FES/5 Ctrlsl</td>
<td>not available not available 27 (DOI 1)/28 4</td>
<td>2</td>
<td>5 mm, 2-mm gap</td>
<td>ROI manual tracing</td>
<td>left lateral ventricle left and right cerebral hemispheres right cerebellum</td>
<td>(±) 3.0 (±) 0.4</td>
<td>(−) 1.3/ (−) 0.4/</td>
<td>(−) 1.0</td>
</tr>
<tr>
<td>Gharabeh et al., 2000</td>
<td>55 (33 became chronic SZ) 22 Ctrlsl</td>
<td>27 (DOI 1) 3.7</td>
<td>3.7</td>
<td>5 mm, 2-mm gap</td>
<td>geometric morphometric assessment</td>
<td>progressive midline-structure shape change in patients but not in Ctrlsl</td>
<td>(−) 2.2 (−) 0.9</td>
<td>(−) 1.1 (±) 2.1</td>
<td>right and left hippocampus/amygdala right and left caudate nuclei</td>
</tr>
<tr>
<td>Nair et al., 1997</td>
<td>18 chronic SZ 5 Ctrlsl</td>
<td>26</td>
<td>4</td>
<td>1.95 mm</td>
<td>semiautomated measurement</td>
<td>right and left ventricles (all patients) (patients can be divided into 2 clusters: 1 with normal and the other with significant ventricular expansion)</td>
<td>(±) 9.2 (±) 3.3</td>
<td>others not examined</td>
<td>correlations were not found</td>
</tr>
<tr>
<td>Keshavan et al., 1998</td>
<td>11 SZ 12 Ctrlsl</td>
<td>24 24</td>
<td>1</td>
<td>2.6 mm</td>
<td>semiautomated segmentation and ROI manual tracing</td>
<td>right STG (follow-up volume compared with baseline volume)</td>
<td>(±) 11.5 (±) 4.6</td>
<td>left STG volume increase in STG might reflect anti-psychotic effect</td>
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### Table 1. Continued

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<th>% Change/Year</th>
<th>Brain Regions Showing Corresponding % Changes/Year in Ctrls</th>
<th>Brain Regions Showing Corresponding % Changes/Year in Patients</th>
<th>Correlations Among Brain Changes, and With Other Clinical Variables</th>
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<tbody>
<tr>
<td>Gur et al., 1998</td>
<td>40 SZ (20 FES/20 treated) 17 Ctrls</td>
<td>29 (28/31)</td>
<td>2.48</td>
<td>5 mm ROI manual tracing</td>
<td>left frontal</td>
<td>(-) 1.7</td>
<td>not reported</td>
<td>whole brain</td>
<td>greater frontal and temporal reduction correlated with less improvement in negative symptoms and hallucinations in FES, with improvements in most positive symptoms in both FES and treated patients and with higher dose of medication in FES</td>
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<td></td>
<td></td>
<td>29 (DOI 2.8/8.5)</td>
<td></td>
<td></td>
<td>right frontal</td>
<td></td>
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<td></td>
<td></td>
<td>32</td>
<td>2.72</td>
<td></td>
<td>left temporal (reduction SZ &lt; Ctrls)</td>
<td>(-) 1.1</td>
<td>not reported</td>
<td>CSF</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>right temporal (reduction SZ &lt; Ctrls)</td>
<td>(-) 1.1</td>
<td></td>
<td></td>
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<tr>
<td>Davis et al., 1998</td>
<td>53 chronic SZ (22 Kraepelinian, 31 non-Kraepelinian) 13 elderly Ctrls</td>
<td>40 (42 and 38, respectively)</td>
<td>5</td>
<td>CT 8 mm semiautomated measurement</td>
<td>lateral ventricles (Kraepelinian SZ versus non-Kraepelinian SZ)</td>
<td>(+) 4.0</td>
<td>(+) 0.2 in non-Kraepelinian</td>
<td>others not examined</td>
<td>correlations were not found</td>
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<td></td>
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<td>60</td>
<td>5.3</td>
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<td>Madsen et al., 1999</td>
<td>21 FES/10 psychiatric 9 Ctrls</td>
<td>27</td>
<td>5</td>
<td>CT 8 mm preset density discrimination</td>
<td>frontal (increased sulcal prominence) ventricles (ventricle: brain ratio increase)</td>
<td></td>
<td></td>
<td></td>
<td>atrophy was related to continuous psychosis or lifetime dosage of neuroleptics</td>
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<td></td>
<td></td>
<td>27</td>
<td>5</td>
<td></td>
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<tr>
<td>Garver et al., 2000</td>
<td>25 (19 SZ, 4 SAP, 1 Aff, 1 NOS) 5 Ctrls</td>
<td>32 (DOI 8.6)</td>
<td>2.3</td>
<td>1.25 mm semiautomated measurement</td>
<td>ventricles (lateral and third together) between 8 patients (similar time 1&amp;2 SAPS) and 5 Ctrls</td>
<td></td>
<td></td>
<td>whole brain (between 8 patients and 5 Ctrls)</td>
<td>worsening of symptoms correlated with decreased ventricular (lateral and third together) and increased total brain volume</td>
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<td></td>
<td></td>
<td>40</td>
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<td>Corresponding % Changes/Year inCtrls</td>
<td>Brain Regions Showing No Change</td>
<td>Correlations Among Brain Changes, and With Other Clinical Variables</td>
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<tr>
<td>Saijo et al., 2001&lt;sup&gt;104&lt;/sup&gt;</td>
<td>15 hospitalized chronic SZ 12Ctrls</td>
<td>38 (DOI 15)</td>
<td>10</td>
<td>9 mm, 1-mm gap (0.2 T)</td>
<td>slicewise thresholding technique</td>
<td>lateral ventricles</td>
<td>(+) 2.3</td>
<td>(+) 0.5</td>
<td>others not examined</td>
<td>trend correlation between ventricular enlargement and BPRS negative subscale scores</td>
</tr>
<tr>
<td>Lieberman et al., 2001&lt;sup&gt;16&lt;/sup&gt;</td>
<td>53 FES/SAP 15Ctrls</td>
<td>26</td>
<td>1.5</td>
<td>3.1 mm (1.0 T)</td>
<td>semiautomated processing, cortex parcellated with planes</td>
<td>cerebral cortex (poor outcome patients)</td>
<td>not reported</td>
<td>not reported</td>
<td>cerebral cortex (all patients) total ventricles (all patients) caudate nuclei hippocampus</td>
<td>total ventricle and cerebral cortex increase correlated with poor outcome; cerebral cortex and hippocampus increase correlated with good outcome; medication effect was not found</td>
</tr>
<tr>
<td>Wood et al., 2001&lt;sup&gt;113&lt;/sup&gt;</td>
<td>30 FE psychotics 12 chronic SZ</td>
<td>22</td>
<td>1.9</td>
<td>1.5 mm ROI manual tracing</td>
<td>whole brain volume loss in FES</td>
<td>not reported</td>
<td>not reported</td>
<td>hippocampus</td>
<td>correlations were not found</td>
<td></td>
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<tr>
<td></td>
<td>12 chronic SZ</td>
<td>34</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>temporal lobe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26Ctrls 24 SZ</td>
<td>24</td>
<td>2.2</td>
<td>0.6</td>
<td>subvoxel registration; semiautomated measurement</td>
<td>none (larger increase and decrease in lateral ventricle)</td>
<td></td>
<td></td>
<td>lateral ventricle</td>
<td>correlations were not found</td>
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<tr>
<td>Mathalon et al., 2001&lt;sup&gt;103&lt;/sup&gt;</td>
<td>24 males chronic SZ 25 control men</td>
<td>39 (DOI 15.3)</td>
<td>3.6</td>
<td>5 mm, 2.5-mm gap</td>
<td>tissue segmentation; ventricles in inner 55%; brain in outer 45%; regional parcellation with orthogonal planes</td>
<td>left and right prefrontal sulci (trend) right prefrontal gray matter right frontal sulci right frontal gray matter</td>
<td>(+) 6.6/ (+) 4.7 (+) 3.6/ (+) 1.6</td>
<td>left prefrontal gray matter faster frontal sulcal expansion correlated with greater BPRS total and positive scores and longer hospitalization; prefrontal gray matter decline and sulcal expansion correlated with greater BPRS total and negative scores; temporal gray matter decline correlated with greater BPRS total and negative scores; medication effect was not reported</td>
<td></td>
</tr>
<tr>
<td>Cahn et al., 2002&lt;sup&gt;105&lt;/sup&gt;</td>
<td>34 FES 36 Ctrl</td>
<td>26 (DOI 14.0)</td>
<td>1</td>
<td>1.2 mm</td>
<td>brain extraction with dual echo; tissue segmentation on T1</td>
<td>whole brain gray matter lateral ventricles</td>
<td>(-) 1.2 (+) 0.01 (-) 2.9 (+) 0.01 (-) 7.7 0</td>
<td>total white matter cerebellum third ventricle</td>
<td>gray matter decline correlated with outcome, and also correlated with cumulative dosage of antipsychotics</td>
</tr>
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<tr>
<td>Ho et al., 2003</td>
<td>73 recent-onset SZ</td>
<td>25 (DOI 2.0)</td>
<td>3.29</td>
<td>T1 1.5 mm</td>
<td>images warped to Talairach space and automatically parcellated into ROIs; tissue segmentation with T1, T2, and PD images</td>
<td>cortical sulcal CSF frontal CSF frontal tissue</td>
<td>(+) 6.6</td>
<td>(−) 1.3</td>
<td>total brain tissue</td>
<td>poorer outcome correlated with greater lateral ventricle enlargement; greater frontal white matter decline and CSF expansion correlated with worse negative symptoms; decline in frontal gray and white matter volume correlated with poorer executive functioning; medication effect was not found</td>
</tr>
<tr>
<td>23Ctrls</td>
<td>27</td>
<td>3.39</td>
<td>T2/PD 3 mm</td>
<td></td>
<td></td>
<td></td>
<td>(-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kasai et al., 2003</td>
<td>13 FES</td>
<td>27 (DOM 1)</td>
<td>1.43</td>
<td>1.5 mm</td>
<td>ROI manual tracing</td>
<td>left posterior STG gray matter of left STG&lt;sup&gt;a&lt;/sup&gt; gray matter of left posterior STG&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(-) 6.6</td>
<td>(−) 0.4</td>
<td>amygdala-hippocampal complex&lt;sup&gt;a&lt;/sup&gt; gray matter of right STG&lt;sup&gt;a&lt;/sup&gt;</td>
<td>the more pronounced the volume decreases, the worse the BPRS measures; medication effect was not reported; no significant volume reduction in STG in FE affective psychosis</td>
</tr>
<tr>
<td>Kasai et al., 2003</td>
<td>15 FE Aff</td>
<td>22</td>
<td>1.48</td>
<td></td>
<td>ROI manual tracing</td>
<td>gray matter of left Heschl gyrus&lt;sup&gt;b&lt;/sup&gt; gray matter of left planum temporale</td>
<td>(-) 4.8</td>
<td>(−) 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Ctrlsl/22Ctrls&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26&lt;sup&gt;a&lt;/sup&gt;/25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.63&lt;sup&gt;a&lt;/sup&gt;/1.57&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(-) 5.0</td>
<td>(−) 0.8</td>
<td>gray matter of right planum temporale&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>McCarley et al., 1999&lt;sup&gt;5&lt;/sup&gt;</td>
<td>9 FES/8 FE Aff/7Ctrls</td>
<td>not available</td>
<td>not available</td>
<td>1.5 mm</td>
<td>ROI manual tracing</td>
<td>gray matter of left STG&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(-)</td>
<td></td>
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<sup>a</sup> Gray matter region of interest.  
<sup>b</sup> Parietal lobe.
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<tr>
<td>Bachmann et al., 2004 [29]</td>
<td>14 FE S/SAP/SF (noCtrls for longitudinal comparisons)</td>
<td>24</td>
<td>1.14</td>
<td>1.8 mm</td>
<td>automated measurements after linear transformation into Talairach space</td>
<td>frontal lobe</td>
<td>none</td>
<td>prefrontal gray and prefrontal white</td>
<td>correlations were not found</td>
</tr>
<tr>
<td>Dickey et al., 2004 [27]</td>
<td>12 FH SZ/10 FH Afl/15Ctrls</td>
<td>28/23/25</td>
<td>1.5</td>
<td>1.5 mm</td>
<td>automated + minimal tracing</td>
<td>none</td>
<td>left lateral ventricle (years 1–10)(^a)</td>
<td>(+) 2.3</td>
<td>right lateral ventricle(^b)</td>
</tr>
<tr>
<td>DeLisi et al., 2004 [99] DeLisi &amp; Hoff, 2005 [100]</td>
<td>26 FES(^a)/ 27 FES(^b)</td>
<td>27 (DOI 1)</td>
<td>4–5 and 10</td>
<td>5 mm, 2-mm gap</td>
<td>ROI manual tracing</td>
<td>left lateral ventricle (years 5–10)(^a)</td>
<td>(+) 3.3</td>
<td>left lateral ventricle (years 5–10)(^b)</td>
<td>hemispheres(^a)</td>
</tr>
<tr>
<td></td>
<td>10Ctrls</td>
<td>26</td>
<td>5 mm, 2-mm gap</td>
<td>ROI manual tracing</td>
<td>left lateral ventricle (years 5–10)(^b)</td>
<td>STG</td>
<td>temporal lobe(^b)</td>
<td>right temporal reduction</td>
<td>greater ventricular change correlated with better outcome</td>
</tr>
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\(^a\) years 1–10 ventricular change correlated with hospitalization time |

\(^b\) years 5–10 ventricular change correlated with better outcome |
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<tbody>
<tr>
<td>Lieberman et al., 2003&lt;sup&gt;14&lt;/sup&gt;</td>
<td>82 olanzapine-treated FE SZ/Aff/SF (O)</td>
<td>24 (DOI 1)</td>
<td>2</td>
<td>1.5 mm T1</td>
<td>automated segmentation and parcellation, caudate manual tracing</td>
<td>whole brain gray (H versus O and H versus C)</td>
<td>(−) 1.7 versus (−) 0.5</td>
<td>(−) 1.7 versus (−) 0.5</td>
<td>whole brain (H versus O)</td>
<td>greater improvements in PANSS total and negative associated with less lateral ventricular increase in olanzapine group</td>
</tr>
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<td>79 haloperidol-treated FE SZ/Aff/SF (H)</td>
<td>24 (DOI 1.5)</td>
<td>3 mm T2 and PD</td>
<td>frontal gray (H versus O and H versus C)</td>
<td>(decrease) H &gt; O H &gt; C</td>
<td>whole brain white matter (H versus O)</td>
<td>less improvement in neurocognitive functioning associated with greater decrease in frontal and parietal gray matter</td>
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<tr>
<td></td>
<td>58 Ctrls (C)</td>
<td>26</td>
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<tr>
<td>James et al., 2002&lt;sup&gt;131&lt;/sup&gt;; 2004&lt;sup&gt;210&lt;/sup&gt;</td>
<td>16 adolescent-onset SZ</td>
<td>17 (DOI 1.5)</td>
<td>2.7</td>
<td>5 mm sagittal</td>
<td>ROI manual tracing</td>
<td>whole brain (trend)</td>
<td>not reported</td>
<td>not reported</td>
<td>lateral, third, and fourth ventricles; temporal lobes; hippocampus; amygdala; cerebellum; anterior vermis; posterior superior vermis; prefrontal; thalamus</td>
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<td></td>
<td>16 Ctrls</td>
<td>16</td>
<td>1.7</td>
<td>3 mm coronal</td>
<td></td>
<td>posterior inferior vermis (trend)</td>
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Table 1. Continued

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<tr>
<th>Investigators</th>
<th>Subject Groups</th>
<th>Average Age of First Scan (years)</th>
<th>Average Years of Follow-up</th>
<th>Image Slice Thickness</th>
<th>Methods of Analysis</th>
<th>Brain Regions Showing Significant Progressive Change in Patients</th>
<th>Corresponding % Changes/Year inCtrls</th>
<th>Brain Regions Showing No Change</th>
<th>Correlations Among Brain Changes, and With Other Clinical Variables</th>
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<tr>
<td>Pantelis et al., 2003&lt;sup&gt;17&lt;/sup&gt;</td>
<td>10 UHR-P</td>
<td>19</td>
<td>1.1</td>
<td>1.5 mm</td>
<td>automated voxel-based analysis of gray matter change (within-group comparisons)</td>
<td>midline cingulate gray matter left parahippocampal gray matter left fusiform gray matter left orbitofrontal gray matter left cerebellar gray matter (gray matter increase in right cuneus)</td>
<td>gray matter in other regions</td>
<td>UHR-N individuals showed left cerebellar gray matter reduction</td>
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<tr>
<td></td>
<td>11 UHR-N</td>
<td>21</td>
<td>1.8</td>
<td></td>
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<td>Job et al., 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>65 high-risk for SZ</td>
<td>21</td>
<td>2</td>
<td>1.88 mm (1.0 T)</td>
<td>voxel-based morphometry analysis</td>
<td>temporal gray matter right frontal gray matter</td>
<td>gray matter in other regions</td>
<td>high-risk individuals having psychotic symptoms showed a different spatial pattern of reductions than those who did not high-risk individuals developing SZ showed a different spatial pattern of reductions than those who did not</td>
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<tr>
<td></td>
<td>19Ctrls</td>
<td>21</td>
<td></td>
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<tr>
<td>Sun et al., 2003&lt;sup&gt;223&lt;/sup&gt;</td>
<td>23 FE psychosis (16 FES)</td>
<td>22 (DOI 0.2)</td>
<td>2</td>
<td>1.5 mm</td>
<td>automated SIENA longitudinal brain surface motion measurement and template-based regional parcellation</td>
<td>whole brain (FE versusCtrls)</td>
<td>(−) 0.05 mm/year</td>
<td>(−) 0.02 mm/year</td>
<td>FE versusCtrls: total white matter; orbitofrontal; lateral occipital surface; lateral temporal; medial temporal; lateral ventricles; third ventricle</td>
<td>brain surface retraction in FE represented a similar spatial pattern to that ofCtrls but was significantly accelerated</td>
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<td>Sun 2005&lt;sup&gt;173&lt;/sup&gt;</td>
<td>11 chronic SZ</td>
<td>33 (DOI 12)</td>
<td></td>
<td></td>
<td></td>
<td>left and right dorsal prefrontal (FE versusCtrls and FE versus chronic SZ)</td>
<td>(−) 0.09/0.10 mm/year</td>
<td>(−) 0.04/0.04 mm/year</td>
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<td>28 Ctrls</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>left (trend) and right motor-premotor (FE versusCtrls)</td>
<td>(−) 0.06/0.08 mm/year</td>
<td>(−) 0.04/0.03 mm/year</td>
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<tr>
<td>12 UHR-P</td>
<td>20</td>
<td>1</td>
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<td></td>
<td></td>
<td>left and right superior parietal (FE versusCtrls)</td>
<td>(−) 0.05/0.05 mm/year</td>
<td>(−) 0.02/0.01 mm/year</td>
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<tr>
<td>23 UHR-N</td>
<td>20</td>
<td></td>
<td></td>
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<td>left and right inferior parietal (FE versusCtrls)</td>
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<td>(−) 0.02/0.02 mm/year</td>
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Note: Aff = patients with affective disorders, Ctrls = healthy controls, SZ = schizophrenia, FE = first episode, FES = first-episode schizophrenia, FH = first hospitalized, NOS = psychosis not otherwise specified, SAP = schizoaffective psychosis, SF = schizopreniform, CSF = cerebrospinal fluid, STG = superior temporal gyrus, DOI = duration of illness at first scan, DOM = duration of antipsychotic medications, ROI = region of interest, SAPS = Scale for the Assessment of Positive Symptoms, BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scales, UHR-P = ultrahigh-risk subjects who became psychotic, UHR-N = ultrahigh-risk subjects who remain nonpsychotic, SIENA = Structural Image Evaluation using Normalization of Atrophy. Segmentation refers to brain tissue and CSF classification; parcellation refers to brain regional subdivision; the magnetic field magnitude of scanners was 1.5 T unless otherwise specified; superscripts are used to differentiate studies and results from the same cohorts.
for a proportion of individuals developing schizophrenia, there is disruption at various stages of early (pre- and perinatal) and late (postpubertal) neurodevelopment, and there is emerging evidence for a further active process occurring before, during, and after illness onset. Thus, schizophrenia is a disorder of early and late brain development, in which genetic and nongenetic influences will be important in understanding the brain structural abnormalities observed. Such findings may also be useful in understanding the neuropsychological deficits and behavioral manifestations seen in schizophrenia.

**Neuroimaging Markers of an Early Neurodevelopmental Insult**

Originally, Weinberger and, separately, Murray and Lewis proposed that schizophrenia is related to a defect in brain development that predisposes patients to a characteristic pattern of brain malfunction in early adult life. In order to explain the delay between an early insult and the onset of symptoms in adolescence, it was hypothesized that the behavioral abnormalities appear later in life, at a time when the maturing brain circuits are placed under functional demand. A key notion of the hypothesis, however, is that the brain structural abnormalities occur pre-birth and are static thereafter. The motor, cognitive, social, and emotional changes that have been described in children who go on to develop schizophrenia may be subtle manifestations of an early neurodevelopmental lesion.

Evidence cited in support of the neurodevelopmental model of schizophrenia includes structural imaging findings of reduced volume of temporal lobe structures, ventricular enlargement, reduced cortical folding, and loss of normal asymmetry, in the absence of any age-related effects, together with a lack of neuropsychological evidence of neurodegenerative changes (e.g., no evidence for cytopathological inclusions, gliosis, or neuronal loss). The lack of gliosis, which is regarded as a necessary neuropathological hallmark of neuronal degeneration, has suggested a pathogenesis that is different from other adult-onset and chronic neurodegenerative diseases. Anomalous brain maturation, which may involve apoptosis or synaptic pruning resulting in loss of interneuronal neuropil, have been put forward as possible mechanisms.

Numerous reviews have presented compelling arguments for an early neurodevelopmental lesion being associated with the later emergence of schizophrenia. The identification of persistent markers of an early neurodevelopmental insult in adult patients has provided useful evidence in support of this hypothesis. Such markers include evidence for the presence of minor physical anomalies, neurological soft signs, and dermatoglyphic anomalies, representing persistent markers of early developmental insult. Findings from the Edinburgh genetic high-risk study suggest that such abnormalities are nonspecific developmental markers, which are not mediated by the genes for schizophrenia. Waddington et al., in their studies of facial features, have identified subtle dysmorphogenesis in patients with schizophrenia and have discussed the close link between development of the face and brain and the relevance of an early lesion to later development. This is an interesting approach that finds support from findings of dysmorphogenesis consequent on a prenatal insult in primates.

While a few studies have found an association between such markers of early insult and brain structural abnormalities in adult patients, other studies have been generally negative (see ). This may be because the regions examined using MRI were not those most relevant to an early lesion and/or that the timing during fetal development of any insult may determine which structures are most affected (e.g., second trimester, versus third trimester, versus perinatal). In a recent imaging study by Seolmen et al., monkeys irradiated at different stages of fetal development (early versus midgestational periods) manifested different patterns of abnormality when scanned as adults. The authors suggest that the earlier insult, which affected fronto-subcortical pathways, provides a better model for their hypothesized thalamic-cortical model of schizophrenia. However, another way to interpret these data is that the nature of brain structural abnormalities observed in schizophrenia may depend on the timing of such lesions during fetal development. This may help explain the heterogeneity of structural imaging findings in schizophrenia.

It is unclear whether neuroradiological studies identifying brain structural anomalies can provide historical markers indicative of an early neurodevelopmental lesion. In this context volumetric studies of various structures are problematic, as size changes over development and may be subject to various influences, including environment or the illness itself, as discussed below. Further, while longitudinal studies in high-risk populations are helpful in identifying change during development, it is difficult to establish a link to an early neurodevelopmental lesion. Anomalies in the complex morphological characteristics of the brain, such as gyral patterning or brain asymmetry, which are determined during fetal life and remain relatively stable thereafter, may be more informative. The development of cerebral asymmetry can be observed as early as the second trimester of life and is clearly observable in the newborn. The link between anomalous asymmetry and neurodevelopmental processes was first raised by Crichton-Brown, while more recently Crow has proposed a detailed theory suggesting an intimate relationship between early neurodevelopmental mechanisms determining brain asymmetry and the disease process in schizophrenia. In accordance with this theory, an absence or reversal of normal anatomical brain asymmetries has been described, mostly
in volumetric studies, particularly of the planum temporale and other temporal lobe structures.\textsuperscript{50-54} However, cerebral volume (which is often used to derive measures of anatomical brain asymmetry) is influenced by a number of factors throughout life,\textsuperscript{55} and recent evidence for progressive changes in this region (e.g.,\textsuperscript{56-57}) suggests that they cannot be used as reliable markers of early insult.

Variations in brain structural/morphological features may provide further potential markers of a neurodevelopmental anomaly. For example, there is a higher reported prevalence of cavum septum pellucidum in schizophrenia,\textsuperscript{58} including first-episode schizophrenia\textsuperscript{59} and childhood-onset cases.\textsuperscript{50} Another example providing such evidence of prenatal disturbances to brain development in patients with schizophrenia is provided by our own work examining the surface morphology of the anterior cingulate cortex (ACC) using magnetic resonance imaging.\textsuperscript{61} Compared with controls, male patients with schizophrenia were less likely to show the “normal” leftward ACC sulcal asymmetry, which was explained by reduced gyral folding in the left ACC. These differences were over and above differences in cortical folding across the entire left hemisphere. Given that sulcal/gyral folding is almost complete by the third trimester of gestation\textsuperscript{46, 62} and remains relatively stable from soon after birth,\textsuperscript{46, 63} these anomalies of ACC folding likely reflect early (prenatal) neurodevelopmental contributions to the etiology of schizophrenia. Further, this evidence also supports the notion that there is an intimate relationship between the mechanisms that determine asymmetrical brain maturation during neurodevelopment and the disease process of schizophrenia.\textsuperscript{49}

These findings were replicated by Le Provost et al.,\textsuperscript{64} have also been identified in childhood-onset schizophrenia,\textsuperscript{65} and are in accord with other work that has also identified cortical morphological anomalies in schizophrenia,\textsuperscript{66-69} thereby representing “signatures” of early neurodevelopmental disruptions. As such it would be expected that these neurodevelopmental anomalies would be apparent in pre-psychotic individuals. We recently examined ACC morphology (pattern of folding as well as cingulate sulcus continuity) in 63 males at ultra high risk (UHR) for the development of psychosis in comparison with 75 healthy male subjects.\textsuperscript{70} Criteria for UHR have been fully described elsewhere.\textsuperscript{71-72} Twenty-one of the UHR subjects developed psychosis over a 12-month follow-up period; however, baseline MRI scans were undertaken prior to illness transition. Compared with healthy controls, the UHR group was more likely to have interruptions in the course of the cingulate sulcus and less likely to have a well-developed paracingulate sulcus in the left hemisphere. The pattern of paracingulate folding again showed the “normal” leftward bias in the healthy controls, which (akin to the case for chronically ill patients) was not observed in the UHR group. However, there was no difference in any of the ACC morphological measures between those UHR subjects who subsequently developed a psychosis and those who did not. While these findings suggest that individuals at high risk of psychosis show abnormalities in ACC morphology, the presence of such abnormalities may not be specific to schizophrenia or psychosis. Further, the paracingulate sulcus is a tertiary sulcus and is therefore less likely to be under genetic control, as suggested by twin studies of sulci and gyri.\textsuperscript{73} Such findings may also be nonspecific and may be found in other neuropsychiatric disorders of neurodevelopmental origin, such as autism.\textsuperscript{74}

Given that the patterns of sulci and gyri are essentially fixed early in life, anomalies of the paracingulate sulcus might be markers of subtle neurodevelopmental deviance caused by environmental or epigenetic factors. These disturbances may often be accompanied by localized disruptions in the vascular supply that alter the delivery of nutrients and thereby affect the ongoing development of this and interconnected regions. Thus, intrauterine injuries have been associated with delayed development of the cingulate region, including increased interruptions in cingulate sulcus continuity.\textsuperscript{75} Interestingly, ultrasound of the cingulate sulcus has historically been used clinically as a noninvasive means to qualitatively index overall brain maturation in the preterm newborn.\textsuperscript{76} Therefore, an examination of ACC morphological complexity may be a useful index of disrupted early neurodevelopment. In a study investigating genetic influences on brain structure in schizophrenia and bipolar disorders, genetic risk for schizophrenia was not associated with ACC volume or with hippocampal volume.\textsuperscript{77} These findings receive support in a further elaboration of the UHR studies in which we examined hippocampal volume and cingulate morphology in the UHR individuals according to familial risk of schizophrenia.\textsuperscript{78} Compared with the UHR group having a positive family history of schizophrenia, those without a family history had significantly smaller left hippocampal volume and a trend toward anomalous left cingulate morphology, with reduced paracingulate folding and more cingulate sulcus interruptions. These findings are consistent with the notion of an early insult of non-genetic origin and may render this region susceptible to later progressive changes as shown recently in longitudinal volumetric studies in high-risk subjects.\textsuperscript{17-18}

In summary, neuroimaging studies that can define anomalies, which are necessarily of early neurodevelopmental origin (e.g., anomalous gyral patterning), may provide an indirect signature for an early neurodevelopmental lesion as etiologically relevant in at least a proportion of patients with disorders such as schizophrenia. However, an issue not adequately dealt with in the available literature is that the nature of any structural abnormalities observed in adulthood, after illness onset, may depend on an interaction between the nature of the insult and the neurodevelopmental stage of the fetus from early gestation to birth.
Evidence for Progressive Brain Changes From Psychosis Prodrome to Established Schizophrenia

While such evidence is consistent with an early neurodevelopmental insult, as discussed in their review of the neuropathological evidence, Harrison and Lewis state that it is the lack of evidence to support a progressive or degenerative process that, "by default, is the stronger pointer towards a neurodevelopmental origin." (p. 318)6 As discussed below, there is now increasing evidence to suggest that progressive neuroanatomical changes do occur in schizophrenia, for several years from its earliest manifestations. However, the extent to which these changes reflect an interaction between the early aberrant neurodevelopmental processes described above and ongoing neurodevelopment in adolescence is unclear. Given that neurodevelopment does not end with birth, a model that incorporates (i) the early (pre- or perinatal) developmental insult with (ii) anomalies of later/ongoing developmental processes such as myelination or synaptic pruning (e.g., 31–32, 79) and (iii) nondevelopmental, possibly neurodegenerative, changes around the onset of the illness is required. We first consider the structural neuroimaging evidence for progressive changes and focus particularly on the earliest stages of schizophrenia.

**Structural Imaging Studies in First-Episode Psychosis and Established Schizophrenia**

The growing number of cross-sectional studies examining the presence and extent of brain structural abnormalities provide evidence for abnormalities in frontal, temporal, and midline limbic structures, as well as the morphological abnormalities mentioned above,1–3 with more severe changes often seen in patients with more chronic forms of the illness. However, whether these abnormalities are pre-existing, occur at a particular stage of the illness, or are associated with its progression is unclear and has been contentious.80–82 Despite the methodological and other issues raised, the most important studies to assess progression are longitudinal within-subject studies that examine patients early in their course and follow them throughout their illness. These studies, summarized in table 1, are difficult to undertake and present a major challenge.

Before reviewing the follow-up studies, it should be acknowledged that information from cross-sectional studies could also be informative about the issue of progression. As eloquently argued by Woods,13 the presence of enlarged cerebrospinal fluid (CSF) spaces, particularly extracerebral CSF, together with findings of reduced brain tissue volume in schizophrenia suggests that progressive changes are occurring, as brain and skull growth are complete early in life before the onset of schizophrenia. Enlargement of the CSF spaces is evident from illness onset83–87 with further progressive changes suggested in cross-sectional studies88–89. In a recent meta-analysis of brain volume studies, Woods et al.90 examine their notion of identifying brain changes before versus after attainment of maximum brain and intracranial volumes (at around 10–13 years; see 91). Based on 20 published studies, involving almost 1,000 patients compared to a similar number of controls, they found that brain volume loss in schizophrenia occurs to a similar degree before and after attainment of maximum brain size. However, such studies are limited, in that the measures are gross, there are limited data about the estimation of maximum brain volume, and the analyses have not examined whether specific brain regions are more or less involved at different phases of the illness or in relation to specific periods of maturation. The advantage of such an approach, however, is that large numbers of patients can be included so that more representative cohorts of patients with schizophrenia can be evaluated. This complements the longitudinal work, in which subject groups have often been small and may not be representative.

While the early longitudinal studies are equivocal regarding progressive brain changes in schizophrenia,92 the better-controlled and more sophisticated studies conducted more recently have more consistently (though not universally) demonstrated such change. Despite this, the numbers in such studies remain generally small, methodologies vary, and the stages of illness examined are relatively limited, most often involving patients with already established schizophrenia. Indeed, many so-called first-episode studies include patients who have already been ill for a number of years. As we discuss below, investigations at the earliest stages of illness, including pre-illness onset, may be critically important to understanding the processes underlying progressive changes.

DeLisi and colleagues have conducted a series of longitudinal MRI studies in a cohort of 50 patients with first-episode schizophrenia/schizoaffective disorder from the beginning of the 1990s, including reports of a 10-year follow-up of 27 patients and 10 control subjects.93–100 In their initial follow-up studies to 5 years, progressive changes were reported in a number of brain regions, including ventricular enlargement, as well as decreased volume of both cerebral hemispheres, the cerebellum, and the corpus callosum, but smaller brain regions such as the amygdalo-hippocampal complex, the caudate nuclei, and the temporal lobes showed no change. In their 10-year follow-up study,99 further ventricular enlargement was observed, and, surprisingly, the increased size of ventricles was associated with better outcome (see below). As in their earlier studies, no change in temporal lobe volume was observed at 10 years.100 It is relevant that in these studies the images obtained had thick slices (5 mm) with an interslice gap of 2 mm, which reduces sensitivity in finding small differences.

Several other longitudinal MRI studies (see table 1) have also focused on the ventricular system, and expansion of ventricles is reported consistently in the more recent work,16,86,101–106 though such changes may be more
relevant to subgroups of patients or relevant to their clinical state. While longitudinal studies examining global changes provide consistent evidence for progressive changes, with enlargement of CSF spaces over at least the first 10 years of illness and brain volume loss, increasingly, studies are focusing on specific brain regions in more detail.

In their longitudinal MRI study of 20 first-episode and 20 previously treated patients with schizophrenia compared with 17 control subjects, Gur and colleagues have found that both patient groups had smaller volumes of frontal and temporal lobes at intake, more pronounced on the left. At follow-up greater reduction in left frontal volume was seen in first-episode schizophrenia patients compared with the other groups. Temporal lobe reduction was greater in first-episode than previously treated patients, but, surprisingly, the reduction in temporal lobes was more pronounced in controls than in patients, a finding that requires further study. Whole brain volume was smaller in patients; however, there were no progressive changes identified for whole brain or CSF volumes. In all groups, greater brain volume reductions were associated with decreased neuropsychological functioning. The relationship with symptoms was more complex but showed parallels with the findings above, in which reductions in frontal and temporal volumes were associated with improvement in some symptoms, including delusions and thought disorder, with temporal lobe reduction being the main unique predictor of clinical improvement. Higher dose of medication was associated with greater volume reduction in the frontal and temporal lobes in first-episode but not previously treated patients. While the sample size was reasonable in this study, thick MRI slices were used, and importantly, the first-episode patients had already been ill for a number of years, and the controls were more comparable in age to the previously treated schizophrenia group. Mathalon et al. have identified similar findings in frontal lobe regions but found additional change in the temporal lobes of patients in their 4-year follow-up study comparing 24 male patients with chronic schizophrenia with 25 controls. Patients showed faster volume decrease in right frontal gray matter and bilateral posterior superior temporal gray matter and faster CSF volume increases in the right frontal sulci, left lateral ventricle, and bilateral prefrontal and posterior superior temporal sulci. These changes were also associated with greater severity of symptoms.

The regions that have received greatest attention in schizophrenia have been the prefrontal cortex and hippocampi and other medial temporal structures, which have been consistently found to be reduced in schizophrenia. Numerous models have been proposed that suggest that the smaller hippocampi are related to early neurodevelopmental lesions and have a relationship with dysfunction of prefrontal cortex.

Lieberman and colleagues undertook a 12-month follow-up of 50 of their 107 first-episode patients and 13 of their 20 control subjects having a baseline MRI. Consistent with findings in other studies, larger ventricles and smaller hippocampi were identified at illness onset, and further ventricular enlargement was observed longitudinally in poor outcome patients. No changes in cortical volume or hippocampal volume were found overall. However, the follow-up period may not have been adequate to detect whole brain volume change, and the sample may not be adequate to assess change in hippocampus; also, the patients were in their mid-twenties, and controls were significantly older.

In our own longitudinal study over a longer follow-up period, we examined whole brain, temporal lobe, and hippocampal volumes. Thirty patients with first-episode psychosis, 12 patients with chronic schizophrenia, and 26 control subjects were followed over a variable period between 1 and 4 years. By examining the rate of change in volumes over the variable follow-up period, progressive reduction in whole brain volume was identified in patients (at a rate of 1–2% per year) but not control subjects. No change was found in temporal or hippocampal volumes, consistent with a number of studies, although reductions in parts of the temporal lobe, specifically the superior temporal gyrus, have been reported in other studies during the early course of the illness. These differences may be explained by relative difficulties in following subjects over a long period, resulting in small samples, and by likely differences in the nature of brain changes at different illness stages, which are considered further below. Similar to our study, Cahn et al. report reductions in total brain volume and cerebral gray matter and ventricular enlargement in their study of 34 first-episode schizophrenic patients and 36 healthy comparison participants over a 1-year follow-up. Clinical outcome was correlated with the brain changes identified, and, importantly, cerebral gray matter reduction correlated with cumulative dose of antipsychotics between scans.

The possibility of a relationship to clinical symptoms or outcome is intriguing, though this relationship seems complex, with some studies showing an inverse relationship indicating that progressive structural changes are associated with better outcome, while Garver et al. have identified clinical state–related changes in ventricles and brain volume. It has been suggested that the loss of brain tissue that may include pathological neural circuits relevant to the symptoms of schizophrenia may explain these findings. While this notion has been criticized, it remains an interesting proposition. However, though studies have attempted to control for the effects of medication statistically, it remains possible that these inverse correlations are explained by the effects of medication in reducing symptoms as well as being causative in producing brain structural abnormalities.
as demonstrated recently (e.g., 114–116). Indeed medication remains a confounding factor in most of the longitudinal studies. Studies have also not taken account of the high rate of alcohol or substance use in schizophrenia, though abuse of these substances is usually an exclusion criterion. Another issue to be considered is the clinical heterogeneity of the cohort being studied. For example, patients with nondeficit compared with deficit schizophrenia are more likely to experience stress and abuse drugs compared to the poorer outcome deficit subgroup (characterized by primary negative symptoms) and are more likely to respond to medication.

Taken together these longitudinal MRI studies are consistent in demonstrating ventricular volume increases and brain volume reductions in schizophrenia, with evidence for cortical gray matter loss, possibly involving specific brain regions, particularly the prefrontal and temporal lobe cortices. The studies also demonstrate variability in findings, which probably relates to relatively small samples, especially for controls; differences in stages of illness, with very few studies at the very earliest phase of schizophrenia; and important differences in age, which may mask changes related to brain maturation in patients and controls. In order to address the latter issue, studies in younger cohorts at the very earliest stages of illness and in the context of understanding brain maturational changes are necessary, as discussed below.

In our most recent follow-up study cortical changes identified in our earlier study were examined in greater detail, by using the same cohorts.113 The first-episode patients in this study had been scanned within the first few weeks of onset of their psychotic illness. We modified and extended a novel technique to identify change at every point on the cortical surface, by assessing whether each point at the boundary between gray matter and CSF at the second scan had moved toward (expansion) or away from (retraction) the skull relative to the boundary established at the time of the first scan. We sought to identify whether the whole brain volume change we identified earlier was global or whether it was related to change in specific cortical regions. Furthermore, we selected those first-episode psychosis patients with schizophrenia ($n = 16$) and identified 2 control groups that were age matched to each of the first-episode and chronic patient cohorts. Following the first episode of schizophrenia, there was a subtle but highly significant degree of surface contraction in frontal (particularly dorsolateral prefrontal) and parietal regions of the cortex in both cerebral hemispheres relative to the changes seen in healthy controls. There was no difference in the rate of change between the chronic schizophrenia and control groups, suggesting that such changes are most prominent at the earliest phase of schizophrenia. However, further study will need to involve larger samples, particularly in the chronic group. The pattern of change was very similar in all 3 groups but was amplified by a factor of almost 3 in both hemispheres in the first-episode patients. The close correspondence between the pattern of structural change following schizophrenia onset and that associated with normal development, as seen in the normal sample, was interpreted as suggestive of a late neurodevelopmental abnormality, manifest as an acceleration of normal processes. These findings are in accord with evidence for frontal volume loss involving gray matter in schizophrenia, including postmortem evidence. However, it should be noted that the methodology allowed examination at a subvoxel level, thereby allowing subtle changes to be detected, which may explain the lack of significant findings in some follow-up studies using region of interest or other methods (e.g., 127, 131). Our results are, however, consistent with the recent and largest 3-year follow-up study by Ho and colleagues, comparing 73 patients with recent-onset schizophrenia and 23 normal controls. They have found increases in cortical sulcal CSF and frontal sulcal CSF as well as shrinkage of frontal lobe tissue. Patients with poor outcome had greater lateral ventricular expansion, while negative symptom severity and poorer executive functions were related to frontal measures of reduced volume. The patients in this study were also comparable to those in our own study in being younger than subjects in other studies and closer to onset of illness. In both studies those having their first hospitalization had received on average only 1 month of antipsychotic treatment, which may be relevant to the potential impact of antipsychotics identified in the recent study by Lieberman et al.

Our findings, demonstrating a similar but accelerated pattern of brain volume loss in early schizophrenia, are in accord with the emerging evidence of normal gray matter volume changes occurring during adolescence and early adulthood and of greater changes in young patients with childhood-onset schizophrenia. These series of studies in a unique population of adolescents with childhood-onset schizophrenia have shown widespread changes in cortical and subcortical regions over a period of 3 to 5 years. With more sophisticated analysis techniques, this cohort showed an age-accelerated gray matter loss that moved in a dynamic pattern across the brain, from parietal regions anteriorly to temporal and then frontal lobes. This pattern of loss was associated with expected patterns of psychotic symptoms and cognitive deficits. Thus, active brain changes may be occurring throughout the early years of psychosis, and the nature and location of brain change may depend on the interaction between the disease process and normal brain development.

In this context, our findings of an accelerated process of gray matter loss over the first few years of onset of schizophrenia may be understood as reflecting aberrant maturation during adolescence or an interaction of early neurodevelopmental insult with the processes of maturation around the time of illness onset in adolescence and...
early adulthood. Recent work examining patients during the prodromal phase of the illness and through the transition to first episode has begun to shed light on possible progressive structural changes as the illness is developing.\textsuperscript{17–18} Such studies may help to unravel the complex interaction between brain structural changes during maturation and the onset of schizophrenia. The limited available studies are reviewed in the next section.

**Structural Imaging Studies in Prodromal/High-Risk Individuals**

Prodromal studies in Melbourne and Edinburgh are the first high-risk studies to investigate brain structure longitudinally in large numbers of young people at risk for the development of psychosis, using MRI to follow them through the period of transition to illness\textsuperscript{17–18} (for reviews, see \textsuperscript{19–21, 144–145}). As discussed by Lawrie,\textsuperscript{145} the approaches in these studies are different but complementary. The Edinburgh strategy has been to recruit young asymptomatic subjects (aged 16–24) with at least 2 affected family members with a confirmed diagnosis of schizophrenia. They have been able to recruit a large cohort (n = 229), with 150 having at least 1 MRI scan.\textsuperscript{145} Similarly aged comparison groups and patients with first-episode schizophrenia (FES) were also recruited. Initial results from the MRI studies during various stages of recruitment include findings of reduced volume of the amygdala-hippocampal complex in presymptomatic cases compared with controls, though not as small as in FES, and smaller thalamus compared with controls.\textsuperscript{146} Voxel-based morphometry (VBM) studies of these groups have confirmed these findings and also identified reductions in anterior cingulate, medial prefrontal, and parahippocampal gray matter volumes, with greater reductions observed in the FES group.\textsuperscript{147–148} While these initial studies are interesting, subjects who were to develop schizophrenia had not yet made the transition to illness. A recent study addressing this issue is discussed below.\textsuperscript{18}

The Melbourne group used a “close-in” strategy to identify those symptomatic, clinically compromised (but subthreshold), and help-seeking individuals at imminent risk of developing a florid psychosis (UHR group).\textsuperscript{149–150} which maximizes the number of participants who make the transition to psychosis (around 30–40% in 12 months).\textsuperscript{71–72} Based on our prior work identifying reduced hippocampal volume in first-episode psychosis and established schizophrenia compared with a large control sample\textsuperscript{151} and based on the neurodevelopmental model, we predicted that smaller hippocampal volumes would be identified in the pre-psychotic high-risk group. Our initial results examining the hippocampi in the UHR group supported these predictions, since in both cases the high-risk group overall had smaller volumes than a comparison population.\textsuperscript{152–153} Similar findings are also reported for the amygdalo-hippocampal complex in the Edinburgh study.\textsuperscript{146} However, this does not necessarily imply that these abnormalities represent lesions associated with psychosis, as not all of these individuals will develop a psychotic illness. Because of the high transition rate to psychosis, the Melbourne group has now reported a number of neurobiological studies examining those UHR individuals who developed psychosis versus those who did not.\textsuperscript{17, 70, 78, 153–160}

In the first study we examined hippocampal and whole brain volumes in 20 “ultrahigh-risk” individuals who developed psychosis (UHR-P) and the 40 who did not (UHR-Nonpsychosis [NP]) compared with 32 first-episode psychosis patients and 139 normal controls.\textsuperscript{153} Contrary to expectation, it was the UHR-NP who had smaller left hippocampal volumes at intake (and were more similar to first-episode psychosis subjects), while the UHR-P group did not differ from a comparable normal sample. Further, the larger (but still normal) left hippocampal volume of the UHR cohort at intake was associated with the subsequent development of acute psychosis, rather than smaller volumes. More recently we have undertaken a much larger study of hippocampal and amygdala volumes involving 473 subjects, including 89 patients with chronic schizophrenia, 162 patients with first-episode psychosis (46 schizophrenia/schizoaffective, 57 schizophreniform, 34 affective, and 25 “other psychoses”), 135 UHR patients (39 UHR-P), and 87 control subjects.\textsuperscript{160} This study extends our work on the hippocampus considerably by including large numbers of subjects and also includes separate estimates of amygdala volumes. As before, patients with chronic schizophrenia had bilaterally smaller hippocampi, while first-episode schizophrenia patients had smaller left hippocampi. However, first-epidsode schizophreniform patients and the UHR groups had normal hippocampal size. In contrast to our previous finding of smaller hippocampal volumes in the UHR-NP group, in this larger sample, hippocampi did not differ from normals. Further, hippocampi were of normal size in patients with affective psychoses or psychosis not otherwise specified, while amygdala volumes were significantly larger in this group. In contrast, all the schizophrenia patients had normal amygdala size. Thus, findings of smaller hippocampi in schizophrenia were confirmed, and these results are consistent with those of other studies including meta-analyses.\textsuperscript{1, 109–110} The finding of increased amygdala size in subjects with nonschizophreniform psychoses including bipolar disorder is also consistent with some of the available literature in such disorders.\textsuperscript{151, 161–162} These findings also suggest that hippocampal and amygdala volumes should be assessed separately, and given that a number of studies measure the 2 together (as in the Edinburgh high-risk study),\textsuperscript{146} this may be an important reason for differences between studies. Our finding of normal size of the hippocampi in the UHR-P individuals...
is also consistent with our previous report, though in this study the UHR-NP also did not differ from normal subjects or from the UHR-P group. It is important to note that as this initial study was cross-sectional, the findings may be a reflection of sampling with the UHR-P group not being truly representative of the whole pre-psychotic population who later become psychotic. It is likely that the larger cohort was important in assessing this effect accurately, though changes in the population recruited over the period of recruitment may also be a factor. The important finding here is that prior to psychosis onset and in recently developed schizophreniform psychosis, the hippocampal volumes are normal, while with greater illness duration smaller volumes are found, initially on the left and later bilaterally. Our findings of normal hippocampal size in UHR groups and at the earliest phase of a first-episode psychosis also receive support from our magnetic resonance spectroscopy study that failed to identify any reduction in N-acetyl-aspartate (considered to index neuronal integrity) in these groups compared with control subjects, in contrast to studies of patients with schizophrenia.

In another VBM study examining a cohort of 34 patients with chronic schizophrenia with variable length of illness between 2 and 31 years, increasing duration of illness was significantly associated with loss of volume in the right medial temporal, medial cerebellar, and bilateral anterior cingulate gray matter volume. We are currently reassessing our first-episode patients in a 10-year follow-up study to examine change in structures including the hippocampus, though no data are currently available.

Our findings challenge the traditional early neurodevelopmental insult theory and raise questions about the possible relationship of progressive changes during late neurodevelopment (in adolescence) to any such proposed early neurodevelopmental insult affecting medial temporal structures. The latter has been proposed as a model to explain the observed abnormalities in hippocampi as well as the prefrontal cortex in schizophrenia. Given this model, hippocampi should be reduced in pre-psychotic individuals. We have previously discussed possible reasons for the apparent normal size of this medial temporal structure, including that (a) the process of transition from an at-risk mental state to acute illness (and from schizophreniform to schizophrenia) is associated with some loss of hippocampal structure; or (b) as predicted by the traditional neurodevelopmental model, the hippocampi of the UHR sample are small initially but immediately prior to the onset of psychosis there is a physiological change that is manifested as an increase in hippocampal size to within normal limits; or (c) there are developmental abnormalities in the hippocampi of people who eventually develop acute psychosis, which make the hippocampal size larger than might otherwise be expected prior to illness onset, resulting in this structure being vulnerable to insult later in life, such as stress-related damage. This explanation is also consistent with the neurodevelopmental model, as this abnormal structure would have been determined early in life. Some support from our own data in our UHR sample is that, regardless of subsequent diagnosis, there was a smaller volume of hippocampus in those with a negative family history of psychosis and schizophrenia, suggesting that an early nongenetic insult may be relevant in making this region vulnerable.

With regard to the possibility of progressive changes in medial temporal structures at the earliest stages of schizophrenia, region of interest techniques have generally failed to find evidence for progressive reduction in hippocampal volume; however, studies have been small, and such volume reduction may relate to specific populations, occur within a small time window, or involve only part of the hippocampus. Shape analysis of the hippocampus may be informative, though there have been no such longitudinal studies to date in schizophrenia.

In the first study to report changes over the transition to psychosis, we used VBM methodology to examine brain structural changes in our UHR groups over the transition phase to illness. In this study, 21 of the 75 UHR individuals who had a baseline MRI scan were followed up with a second MRI scan, either immediately post-psychosis (UHR-P group) or after 12 months (UHR-NP group). The comparison between baseline and follow-up scans for the 2 groups indicates that both showed a reduction of gray matter volume in the left cerebellum. However, in the UHR-P group, an additional 3 regions of the left hemisphere were reduced (a left inferior frontal region, a left medial temporal region that included the parahippocampal gyrus and the fusiform gyrus, and the cingulate bilaterally). These findings provide evidence that active brain changes occur in patients developing schizophrenia, something that could perhaps be prevented, ameliorated, or at least delayed by early intervention during or before the first episode of psychosis.

These initial results are suggestive of progressive (including neurodegenerative) brain changes that would be consistent with clinical changes manifest in these patients. Reduction of the threshold in these analyses also identified changes in dorsal prefrontal regions, which we have now replicated using the approach described earlier to assess expansion or retraction at every point on the cerebral hemisphere. In this study, we have identified accelerated gray matter retraction in UHR-P individuals over the transition to psychosis in the same regions as in first-episode patients, although there was additional retraction in orbital-prefrontal regions, consistent with the earlier findings. Further, the rate of gray matter retraction was significantly associated with proximity to the transition point to psychosis.

In a recent VBM follow-up study from the Edinburgh group, Job and colleagues have examined brain changes over a 2-year period in 65 young adults from their genetic...
high-risk cohort compared with 19 healthy controls. In the high-risk group significant reductions in gray matter density were identified in temporal lobes and in right frontal and right parietal lobes, which were not identified in the controls. Comparing those individuals with transient or isolated psychotic symptoms \((n = 18)\) with those with no such symptoms showed progressive changes in left temporal lobe regions, including the hippocampus. Those individuals at high risk who later developed schizophrenia \((n = 8; 3\) at the time of the second scan, 5 developing schizophrenia subsequent to the second scan) showed reductions in the left inferior temporal lobe, left uncus, and right cerebellum. These changes are broadly similar to those observed in the Melbourne group’s data; however, these findings identify changes in hippocampus as well as other temporal lobe regions and, further, suggest that these changes may be occurring up to 2 years before onset of illness. Importantly, their subjects were all neuroleptic naïve, indicating that medication does not explain these changes.

Stress hormones, such as cortisol, or hypothalamic-pituitary-adrenal (HPA) axis dysregulation have been associated with structural damage to medial temporal structures.\(^{174–176}\) One intriguing possibility to explain these recent findings in high-risk populations is that they result from stress around the time of illness onset and associated disturbance of HPA axis function. We examined this possibility by measuring the size of the pituitary gland in our various patient groups, as an index of HPA axis function,\(^ {159, 177}\) while in more recent preliminary analyses we identified lower cortisol levels associated with becoming psychotic and an inverse relationship between cortisol levels and brain structural measures (unpublished data and \(^ {178–179}\)), which is similar to the findings in post-traumatic stress disorder (see informative discussions in \(^ {176–180}\)). In the first study we found that in comparison with 59 normal controls, first-episode patients \((n = 24)\) showed a 10% increase in the size of the pituitary, while the pituitary in chronic schizophrenia patients \((n = 51)\) was 17% smaller,\(^ {177}\) suggesting that an overactivity of the HPA axis was evident at the earliest stage following illness onset. More interestingly, we recently assessed pituitary volume in 94 previously never-medicated UHR individuals (selected from our larger sample in order to exclude any medication effects) in comparison with 49 control subjects.\(^ {159}\) UHR subjects who later went on to develop psychosis \((UHR-P, n = 31)\) had a significantly larger \((+12\%\); \(p = .001)\) baseline pituitary volume compared with UHR-NP subjects, while the latter also had smaller pituitaries compared with control subjects \((-6\%\); \(p = .032)\). Further, the risk of developing psychosis during the follow-up period increased by 20% for every 10% increase in baseline pituitary volume \((p = .002)\). The implications of this work are that abnormal HPA axis function around the time of transition to psychosis and during its earliest phases is relevant to the changes observed at this time. Further work is currently exploring these relationships, including an animal model examining the effects of early maternal deprivation (as a stressor) combined with corticosterone treatment (later stress) around adolescence and early adulthood.\(^ {181}\)

### Conclusions and Future Directions

In summary, the available data from structural neuroimaging provide evidence to support a number of processes occurring at different stages of neurodevelopment. This includes evidence, first, for an early (pre- or perinatal) neurodevelopmental lesion that may render the brain vulnerable to anomalous late (particularly postpubertal) neurodevelopmental processes, as indicated by evidence for accelerated loss of gray matter and aberrant connectivity particularly in prefrontal regions; and second, that these anomalous neurodevelopmental processes interact with other causative factors associated with the onset of psychosis (e.g., substance use, stress, and dysregulation of HPA axis function), which together have neuroprogressive sequelae that may be neurodegenerative, involving medial temporal and orbital prefrontal regions, as suggested by imaging studies around transition to active illness. In this context, the features of schizophrenia, including the neuropsychological deficits and behavioral manifestations, can be understood as direct effects of these multiple pathological processes at various neurodevelopmental stages, as we have previously argued.\(^ {19–20, 182–184}\)

The available evidence suggests that neuropsychological functions are not progressive after illness onset and may improve.\(^ {185–189}\) Further, more recent findings from the UHR studies indicate that deficits, particularly of executive functions, are evident before illness onset.\(^ {155–156, 158}\)

**One possible explanation is that there is “development arrest” of those functions that should be developing during adolescence, namely, frontal executive abilities. We have elaborated on these notions elsewhere.\(^ {19–20, 182–184}\)**

The implications of these findings are that, while an early neurodevelopmental lesion may be acting in a proportion of patients subsequently developing schizophrenia, it does not fully explain the active changes occurring during the earliest stages of the illness. Further longitudinal data are necessary from the earliest stages of schizophrenia, particularly in pre-psychotic individuals, together with improved understanding of the brain structural changes during normal development in order to elucidate the exact nature, severity, and timing of the changes seen and their functional sequelae.

It is likely that different processes are involved in the progressive changes described above. Preliminary evidence would support the possible role of stress and disturbances of HPA axis function as relevant to the period of transition to illness and the changes observed in medial temporal, limbic, and orbitofrontal regions. A number of...
other factors must also be considered in future studies, including the impact of substance use, poor diet and exercise, smoking, psychosocial and socioeconomic influences, and associated physical comorbidity, as well as medications other than antipsychotics. Further work needs to examine what neuropathological processes are occurring at this time and whether premorbid stressful events (e.g., obstetric complications, viruses, hypoxia, and other insults during fetal development) may sensitize the individual to the detrimental effects of stress later in life. This has certainly been demonstrated for other medical illnesses, in which stress may be important.\textsuperscript{190} Longitudinal studies in high-risk populations that employ other imaging techniques, such as phosphorus spectroscopy,\textsuperscript{191–193} diffusion tensor imaging, and magnetization transfer imaging,\textsuperscript{195–197} may provide insights about the nature of the changes observed.

Finally, while beyond the scope of this article, genetic influences\textsuperscript{22–23} are an important dimension relevant to understanding these structural abnormalities. Studies examining the influence of genetic load for schizophrenia on such changes have suggested that it is patients with negative family history who are more likely to manifest structural abnormalities, including enlarged ventricles\textsuperscript{196–199} and other cortical and subcortical gray matter abnormalities.\textsuperscript{219, 280} However, this relationship is likely to be more complex, as demonstrated recently.\textsuperscript{201–203} For example, in their study of patients, unaffected siblings, and controls, derived from a Finnish birth cohort, Cannon and colleagues have found that fetal hypoxia is associated with gray matter changes and extracerebral CSF enlargement in patients and siblings but not in control subjects, while only patients showed this relationship with ventricular enlargement.\textsuperscript{202} These findings can be interpreted as indicative of an interaction of early insults and genetic influences that affect later brain development, and they argue for the need to consider the interplay of various likely etiological factors in understanding the evolution of brain structural as well as functional deficits in schizophrenia. The relative contributions of genetic versus nongenetic influences on brain structural abnormalities may also vary, with medial temporal regions being more susceptible to noxious insult, while progressive changes in prefrontal regions may be more influenced by genetic factors.\textsuperscript{21} Given the importance of the early and late neurodevelopmental processes outlined above, genes relevant to such maturational processes are likely to be important candidates for further work. For example, recent molecular biological findings suggest that multiple genes influence brain maturational processes at different stages of brain development and may act as modulators in the emergence and progression of psychosis. These include genes important for brain development, apoptosis, myelination, regulation of synaptic plasticity, G-protein-coupled neurotransmission, and other factors.\textsuperscript{22–33, 204} Future longitudinal investigations need to take account of gene–environment interactions, involving not only possible genes for schizophrenia but the genes relevant to brain maturation.

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References


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