Progressive Changes in the Development Toward Schizophrenia: Studies in Subjects at Increased Symptomatic Risk

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Introduction

Although the underlying neurobiology of emerging psychotic disorders is not well understood, there is a growing conviction that the study of patients at clinical high risk for the illness will provide important insights. Further, a better understanding of the transition period may help the development of novel therapies. In this review, we summarize the extant neuroimaging and neuropsychological studies of people at clinical high risk for psychosis. By and large, there are few definitive markers that distinguish those who do not develop the illness from those who do. The 2 most consistently abnormal brain regions in schizophrenia research, the hippocampi and the lateral ventricles, are not significantly different from healthy controls prior to psychosis onset. However, frontal lobe measures (eg, cortical thickness in the anterior cingulate) do show promise, as do cognitive measures sensitive to prefrontal cortex dysfunction. Further, longitudinal magnetic resonance imaging findings in individuals at ultrahigh risk for developing a psychotic illness show that there are excessive neuroanatomical changes in those who convert to psychosis. These aberrant changes are observed most prominently in medial temporal and prefrontal cortical regions. While the pathological processes underlying such changes remain unclear, speculatively they may reflect anomalies in genetic and/or other endogenous mechanisms responsible for brain maturation, the adverse effects of intense or prolonged stress, or other environmental factors. Active changes during transition to illness may present the potential to intervene and ameliorate these changes with potential benefit clinically.

Key words: neuropsychology/neuroimaging/neurodevelopment

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disorder, or a personal history of schizotypal personality disorder, and significant recent functional decline.

It is still unclear exactly what pathophysiological process underlies the transition from UHR to frank psychosis (or if there are many such processes) and whether this can be detected prior to illness onset. In this review, we discuss potential predictive markers of later psychosis from both neuroimaging and neuropsychological studies, focusing specifically on studies of individuals at clinical high risk. The vast majority of these studies are our own, although there are reports from other centers now being published. This article does not review studies of people solely at genetic high risk.

We begin by examining the extant cross-sectional neuroimaging and neuropsychological studies that aimed to distinguish UHR patients who later developed psychosis from those who did not. The majority of this work has focused on either the medial temporal or frontal lobes, and discussion of these findings make up the bulk of the review. We then briefly examine the evidence for the involvement of other brain regions, followed by a review of the 3 existing longitudinal studies of UHR patients. To aid the reader, we have included a summary table of all neuroimaging studies in UHR cohorts (provided they contain data concerning transitions) (table 1).

Cross-Sectional Studies

Medial Temporal Regions

Our initial studies in schizophrenia and early psychosis focused on medial temporal structures, particularly the hippocampus, because various meta-analyses have consistently reported this region to be reduced in volume, as well as showing neuropsychopathological abnormalities. Furthermore, cognitive abilities thought to rely on the integrity of this region are also impaired. This evidence suggested that hippocampal abnormalities such as reduced size and impaired episodic memory were potential premorbid markers of illness. However, such predictions have not been borne out in our data. Although our early cross-sectional study reported smaller hippocampal volumes in the UHR group as a whole, our recent, much larger study did not support this. Furthermore, no differences were identified between those participants who later developed psychosis (UHR-P) and those who did not (UHR-NP), suggesting that smaller hippocampal volume may not be predictive of later psychosis, but instead be a result of non–illness-specific events, such as obstetric complications. These findings are supported by 2 further studies from our group. First, we found that hippocampal volumes tended to be smaller in UHR patients without a family history of schizophrenia, indicating nonspecific environmental influences on the region. Second, using magnetic resonance spectroscopy (MRS), we (and others) have shown that, compared with control subjects, the UHR group do not exhibit any reduction in left hippocampal N-acetylaspartate (NAA), a marker of neuronal integrity.

We have also examined hippocampal function through cognitive testing, specifically through paired-associate learning. In such tasks, 2 unrelated stimuli (eg, semantically unrelated words or an object and a location) are presented together, and the subject must remember the association. Our published work on verbal paired-associate learning demonstrates no impairment in the UHR group, while unpublished data from a visuospatial paired-associate task also indicate normal hippocampal function prior to transition (L. C. Simpson, unpublished Dpsych thesis).

Despite these findings, a very recent voxel-based morphometry (VBM) study does show hippocampal abnormalities in a UHR population. Borgwardt and colleagues used VBM to compare 22 controls and 35 UHR patients (12 of whom developed psychosis over the following 2 years). Significantly reduced gray matter (GM) volume was found in a number of regions, including the left hippocampus, but there were no hippocampal differences between those who did and those who did not later develop psychosis. It should be noted, however, that these hippocampal differences were only apparent after relaxing the significance level of the analysis and that the use of VBM has been criticized because of its inadequacy in dealing with problems of brain registration. The choice of smoothing kernel is also important, because the size of the kernel should be roughly the size of the difference one expects to see, and varying it may give markedly differing results.

Frontal Cortex

The prefrontal cortex seems the most promising brain region in terms of prediction of later psychosis. The most consistent cognitive findings are of impairments on tasks tapping prefrontal cortical function, such as spatial working memory, antisaccade eye movements, olfactory identification, and tasks requiring rapid processing of information such as story recall. UHR-P patients show specific deficits on all these tasks when compared with those who do not become ill. This pattern of deficits may be the result of reduced GM density in prefrontal regions (although this has not been replicated). There is also evidence for hypofunction of the prefrontal cortex, both from a large (n = 30) MRS study and from a functional imaging study using a visual oddball task. However, these 2 findings are not reported to be specific to those who make the transition to psychosis.

One prefrontal region that has been the focus of great interest in schizophrenia research is the anterior cingulate cortex (ACC), owing to its role in cognitive and emotional processing and strong data from neuropsychopathological studies. Our initial investigations concentrated on the pattern of cortical folding in this region because this is typically established during the early stages of
Table 1. Neuroimaging Studies in Clinical High-Risk Populations

<table>
<thead>
<tr>
<th>Article</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Cross-sectional studies</strong></td>
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<tr>
<td>Phillips et al(^{19})</td>
<td>UHR-P = 20</td>
<td>Volume of hippocampus and whole brain</td>
<td>UHR vs CTRL: UHR ↓ hippocampus bilaterally and whole brain; UHR-P vs UHR-NP: UHR-P ↑ left hippocampus</td>
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<tr>
<td>UHR-NP = 40</td>
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<tr>
<td>CTRL = 139</td>
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<tr>
<td>Pantelis et al(^{15})</td>
<td>UHR-P = 23</td>
<td>VBM of GM</td>
<td>UHR-P vs UHR-NP: UHR-P ↓ GM in right medial temporal lobe, STG, temporal pole, inferior frontal gyrus, VLPFC, and basal ganglia</td>
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<tr>
<td>UHR-NP = 52</td>
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<tr>
<td>Wood et al(^{23})</td>
<td>UHR-P = 6</td>
<td>(^3)H MRS in left medial temporal and left prefrontal (NAA/Cr and TMA/Cr)</td>
<td>UHR vs CTRL: UHR ↑ NAA/Cr and TMA/Cr in prefrontal voxel (interpreted as ↓ Cr)</td>
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<tr>
<td>UHR-NP = 24</td>
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<td>CTRL = 21</td>
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<tr>
<td>Yücel et al(^{51})</td>
<td>UHR-P = 21</td>
<td>Presence or absence of the PCS</td>
<td>UHR vs CTRL: UHR ↓ PCS frequency in left hemisphere; ↑ number of CS interruptions</td>
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<tr>
<td>UHR-NP = 42</td>
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<tr>
<td>Walterfang et al(^{55})</td>
<td>UHR-P = 23</td>
<td>VBM of WM</td>
<td>UHR-P vs UHR-NP: UHR-P ↓ WM in left superior frontooccipital fasciculus (near premotor cortex) and left superior longitudinal fasciculus (near frontal operculum)</td>
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<tr>
<td>UHR-NP = 52</td>
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<tr>
<td>Garner et al(^{66})</td>
<td>UHR-P = 31</td>
<td>Pituitary volume</td>
<td>UHR vs CTRL: not reported</td>
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<tr>
<td>UHR-NP = 63</td>
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<td>CTRL = 49</td>
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<tr>
<td>Jessen et al(^{24})</td>
<td>UHR-P = 3</td>
<td>(^3)H MRS in left frontal, left STG, and bilateral ACC</td>
<td>UHR vs CTRL: UHR ↓ NAA in frontal and ACC voxels</td>
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<tr>
<td>UHR-NP = 16</td>
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<td>CTRL = 24</td>
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<tr>
<td>Velakoulis et al(^{20})</td>
<td>UHR-P = 39</td>
<td>Volume of hippocampus, amygdala and whole brain</td>
<td>UHR vs CTRL: UHR ↓ whole-brain volume</td>
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<tr>
<td>UHR-NP = 96</td>
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<tr>
<td>CTRL = 87</td>
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<tr>
<td>Borgwardt et al(^{27})</td>
<td>UHR-P = 12</td>
<td>VBM of GM</td>
<td>UHR vs CTRL: UHR ↑ GM in bilateral parahippocampal, fusiform, and medial occipital gyri, plus the posterior temporal, inferior parietal and postcentral cortex, the red nucleus and thalamus, and the right supramarginal gyrus</td>
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<tr>
<td>UHR-NP = 23</td>
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<td>CTRL = 22</td>
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<tr>
<td>Berger et al(^{53})</td>
<td>UHR-P = 39</td>
<td>Lateral ventricular volume</td>
<td>UHR vs CTRL: no significant differences</td>
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<tr>
<td>UHR-NP = 96</td>
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<td>CTRL = 87</td>
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<tr>
<td>Fornito et al (unpublished data)</td>
<td>UHR-P = 35</td>
<td>ACC volume, thickness, and surface area</td>
<td>UHR vs CTRL: not reported</td>
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<tr>
<td>UHR-NP = 35</td>
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<td>CTRL = 33</td>
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<tr>
<td><strong>Longitudinal studies</strong></td>
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<tr>
<td>Pantelis et al(^{15})</td>
<td>UHR-P = 10</td>
<td>VBM of GM</td>
<td>UHR-P ↓ bilaterally in cingulate and in left medial temporal, orbitofrontal, and cerebellar regions</td>
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<tr>
<td>UHR-NP = 11</td>
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<tr>
<td>Walterfang et al(^{55})</td>
<td>UHR-P = 10</td>
<td>VBM of WM</td>
<td>UHR-P ↓ deep left parietal WM near frontooccipital fasciculus and left occipital WM subadjacent to calcarine cortex; ↑ posterio cerebellum bilaterally</td>
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<tr>
<td>UHR-NP = 11</td>
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</tr>
<tr>
<td>Sun et al(^{57})</td>
<td>UHR-P = 12</td>
<td>VBM of cortical surface motion</td>
<td>UHR-P ↓ right prefrontal region compared with UHR-NP</td>
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<tr>
<td>UHR-NP = 23</td>
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*Note: UHR-P, ultra high-risk psychotic; UHR-NP, ultra high-risk nonpsychotic; CTRL, control; VBM, voxel-based morphometry; GM, gray matter; STG, superior temporal gyrus; VLPFC, ventrolateral prefrontal cortex; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; Cr, creatine and phosphocreatine; TMA, trimethylamine; PCS, paracingulate sulcus; CS, cingulate sulcus; WM, white matter; ACC, anterior cingulate cortex.*
neurodevelopment (mostly in utero), and so any abnormalities would be consistent with an early neurodevelopmental insult.\(^{39,40}\) We found that, 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.\(^{41}\) This pattern represents a loss of the “normal” leftward bias that we previously identified\(^{42}\) and is similar to that observed in patients with chronic schizophrenia.\(^{43}\) However, there was no difference in any of the ACC surface morphological measures between UHR-P and UHR-NP patients. This suggests that the presence of such abnormalities may not confer specific risk for schizophrenia or psychosis but rather reflect a more general vulnerability to psychopathology. This line of argument is supported by our recent finding of ACC folding abnormalities in people with bipolar affective disorder,\(^{44}\) although this patient group showed a bilateral, rather than left-lateralized folding reduction. It should also be noted that neurocognitive tests sensitive to cingulate dysfunction, such as the Stroop,\(^{45}\) and the continuous performance test-identical pairs,\(^{46}\) do not show differential impairments in UHR patients depending on psychosis outcome.\(^{34,47}\) However, these measures are not especially good indicators of cingulate function,\(^{48}\) and additional study using other tasks is warranted.

There are a number of reports where anterior cingulate related measures do provide predictive markers. The first is an MRS study of 19 UHR patients that found significant reduction in NAA in the cingulate region bilaterally.\(^{24}\) NAA reductions were not predictive of later transition to psychosis—instead, trimethylamines were higher in the later psychotic group indicative of higher rates of cell membrane turnover.\(^{49}\) Because only 3 patients developed psychosis in this study, it is unclear how reliable the finding is and, furthermore, the metabolite ratios were not corrected for differences in GM contribution to the voxel, potentially confounding the results. Nonetheless, the idea that the cingulate might be somehow different in those who make the transition to illness is supported by our own cross-sectional VBM study, which demonstrated significantly reduced GM density in the paracingulate sulcus and tested for differences in the cortical thickness of various subdivisions of the ACC (A. Fornito, A. R. Yung, S. J. Wood, L. J. Phillips, B. Nelson, S. Cotton, D. Velakoulis, P. D. McGorry, C. Pantelis, M. Yücel, unpublished data). We found that, relative to healthy controls, UHR-P individuals showed bilateral thinning of a rostral paralimbic ACC region, and this thinning was correlated with an increased level of negative symptoms. Similar results were found when UHR-P and UHR-NP patients were compared, although in this analysis the thinning was in the limbic region. Interestingly, analysis of subdiagnostic differences in our ACC data suggested that these changes were largely driven by individuals who developed a schizophrenia-spectrum psychosis, with no differences being noted in those that developed a nonschizophreniform (primarily affective) psychosis.

### Other Brain Regions

A number of other regions have been investigated as potential markers of later transition. Enlargement of the lateral ventricles has been suggested, given that it is the first and most consistently reported brain abnormality in schizophrenia research.\(^{52}\) However, our data from 135 UHR patients (39 of whom transitioned to psychosis) reveal no such enlargement prior to the onset of illness.\(^{53}\) Similarly, amygdala involvement has been proposed, based on reductions in chronic illness\(^{52}\) and its role in emotional processing.\(^{54}\) We have reported that amygdala volume is not significantly smaller in UHR patients, with no difference between UHR-P and UHR-NP patients.\(^{20}\) These nonsignificant reductions are larger than those seen for the hippocampus, but this may merely reflect the high prevalence of affective symptomatology in this cohort.

Some unexpected brain regions have been identified as markers of later transition. In both published VBM studies of GM,\(^{27,35}\) right superior temporal gyrus and right insula GM volumes were found to be smaller in the UHR-P group compared with the UHR-NP patients. Further, there were large regions of significantly greater GM volume in the UHR-P individuals, covering the parahippocampal, fusiform, and medial occipital gyri bilaterally, as well as the thalamus, right supramarginal gyrus, and the posterior temporal, inferior parietal, and postcentral cortex bilaterally.\(^{27}\) Similarly, we have identified greater white matter volume in UHR-P individuals in left superior frontooccipital fasciculus (near premotor cortex) and left superior longitudinal fasciculus (near frontal operculum), compared with UHR-NP individuals.\(^{35}\) However, it is unclear what role volumetric increases might play in vulnerability to psychosis, and these findings will need to be replicated in larger samples.

### Longitudinal Changes

All the studies referred above were cross-sectional in design. However, as with detecting dementia, it is possible that change over time may turn out to be the most...
important metric with regard to the later onset of psychosis. Our first study reported significant neuroanatomical changes over the transition to psychosis in cingulate, medial temporal, and orbitofrontal regions, using VBM. Although these changes were not found in UHR patients who did not develop psychosis between the 2 scans, the group-by-time interaction term was not significant. In a similar VBM study of white matter, we have found reductions in deep left parietal white matter near the fronto-occipital fasciculus and left occipital white matter sub-adjacent to calcarine cortex, along with increases in the posterior cerebellum bilaterally. It should be noted, however, that there are a number of methodological limitations to both studies, including small numbers, the use of relatively thick slices that may hinder detection of subtle changes, and the aforementioned problems of brain registration. We have attempted to deal with these limitations by using a different approach that assesses expansion or retraction at every point on the lateral surface of the cerebral hemispheres, combined with cortical pattern matching techniques developed by Toga and Thompson. These more sensitive analyses demonstrated significantly greater brain contraction in the right prefrontal region specific to the UHR-P group, indicative of an accelerated rate of GM retraction in prepsychotic UHR individuals during the transition to psychosis. Interestingly, the pattern of longitudinal change seen in the UHR-P group was similar to that observed in healthy controls, albeit exaggerated in magnitude, suggesting that the transition to psychosis is associated with an exacerbation of normal neurodevelopmental processes. Further, the rate of GM retraction was significantly associated with proximity to the transition point to psychosis. Such work awaits replication with larger cohorts—in particular, the addition of a control group and investigation of possible medication-related effects would be important advances.

The progressive changes we have identified across the transition to psychosis in the right prefrontal region are reflected in a small longitudinal study of cognitive performance. Sixteen UHR patients (7 of whom developed psychosis) were assessed neuropsychologically at baseline and after transition to psychosis (or after 12 months). While performance on most tests was stable or improved, we found that visuospatial memory, verbal fluency, and attentional switching all showed significant decline over the transition to psychosis. These progressive impairments were not seen in the nonpsychotic UHR group. These data indicate that the onset of psychotic disorder is associated with additional impairment in visuospatial and executive abilities that mirrors the progressive changes identified on neuroimaging.

It remains unclear what might cause these progressive changes. One possibility is that they result from stress around the time of illness onset and an associated disturbance of hypothalamic-pituitary-adrenal (HPA) axis function. There is good evidence for an association between stress hormones, such as cortisol, and structural damage to medial temporal regions, as well as the ACC. In recent preliminary analyses in a small UHR sample, we have identified that cortisol levels were associated with the level of depression and anxiety, but not psychotic symptoms. An alternative, indirect index of HPA axis dysfunction can be obtained by examining pituitary volumes on MR images. We measured the pituitary in 94 UHR individuals (selected from our larger sample in order to exclude effects of medication) and 49 control subjects. UHR subjects who later went on to develop psychosis had pituitaries that were 12% larger on average than UHR-NP subjects—furthermore, the risk of developing psychosis during the follow-up period increased by 20% for every 10% increase in baseline pituitary volume. This work suggests that abnormal HPA axis function around the time of transition to psychosis and during its earliest phases may drive some of the brain changes seen in prefrontal and medial temporal regions. Further longitudinal studies as well as investigations assessing the impact of stress and other etiological factors around the time of illness onset will be important to understand the mechanisms underlying the changes in brain structure; some of these are already underway, including studies from our group that are assessing limbic and other cortical regions in detail.

Summary and Conclusions
As yet, there are no convincing, replicated, reports of neuroimaging measures that predict the subsequent onset of psychosis. Instead, the most promising findings have been in the neuropsychological domain, with strong evidence for impairments of prefrontal cortex function in later psychotic patients. However, there are still no clear replications of previously published studies (for review, see Brewer et al), and there is insufficient evidence to recommend a specific screening instrument. Longitudinal studies show promise but raise questions about exactly when the changes in brain structure and function occur with respect to the development of psychopathology.

The relative failure of neuroimaging measures to predict transition to psychosis suggests that standard volumetric techniques are incapable of capturing the subtle differences between UHR individuals with different outcomes. Indeed, the findings with the best predictive power are those looking for small changes in cortical thickness (Fornito et al, unpublished data). Spectroscopy has the potential to detect differences in brain metabolites, including neurotransmitters such as glutamate and gamma-aminobutyric acid, and is therefore a plausible technique for predicting transition. There is a large range of normal physiologic variation, however, so its capacity for separating 2 groups who may only differ marginally may be limited. The most promising technique is functional
magnetic resonance imaging because it combines neurobiology with cognition. However, to date, there has only been one study in a UHR cohort, with no data about transitions, and in any case, it is still unclear whether an activation/deactivation paradigm (as opposed to resting state) will be successful in predicting transition. The combination of functional imaging with spectroscopy has proved informative in other disorders, such as addiction and OCD—incorporating additional modalities, such as diffusion tensor techniques and alternative analysis methods, such as machine learning (eg, Chen et al) seems warranted.

Overall, the investigation of symptomatic high-risk groups has challenged the prevailing models of schizophrenia. The initial results are suggestive of excessive (including neurodegenerative) brain changes that may be consistent with the clinical changes manifest in these individuals as they develop frank psychosis. However, potential markers of impending psychosis need to be considered cautiously and in the context of normal changes occurring at this illness stage. These changes are evident in more posterior regions during childhood and progress anteriorly with the greatest impact apparent in prefrontal regions during adolescence and early adulthood, including increased myelination, synaptic proliferation and pruning, as well as subtle loss of GM volume.

Further, we have previously suggested that there may be a number of processes underlying the observed abnormalities and dynamic changes in early psychosis. In particular, we have argued for 3 processes that would be consistent with the findings to date, including early neurodevelopmental anomalies, progressive changes around the time of transition to illness related to the effects of stress hormones, and changes during the early stages of psychosis relating to alterations of the normal maturational processes (in both cognitive and neuroanatomical measures). Further studies are required to establish the veracity of this proposal and the degree of interaction between these processes and the genetic and social environment. If there are active brain changes occurring as the illness itself is emerging, it is possible that these changes could be prevented, ameliorated, or at least delayed by early intervention, eg, to reduce the impact of stress and stress-related hormones. Preliminary studies suggest that intervention at this early stage may reduce transition to psychosis, including a promising pilot study of low-dose lithium that demonstrates beneficial changes in the hippocampus in an UHR sample. Such data will require replication and increased numbers of subjects.

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