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

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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 go on to develop the illness from those who do not. 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 ultra high 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.

Introduction

The longitudinal investigation of individuals at increased clinical risk for developing psychosis has provided clinical, cognitive, and neuroimaging insights into the period of transition from the at-risk state to the illness/psychosis state. The identification of such cohorts has either focused on positive symptoms (eg, Yung and McGorry1) or the German approach of self-recognized “basic symptoms”12 (for review, see Philips et al13 and Olsen and Rosenbaum). In both strategies, there is a focus on “help-seeking” adolescents, who by definition may already be manifesting established signs of attenuated onset of psychosis, because these state-based criteria are thought to identify an at-risk mental state. These approaches reflect a “close-in” method for identifying a high-risk cohort, where an individual must meet a number of criteria to be included in the high-risk group. Importantly, this maximizes the number of participants who make the transition to psychosis (30%–40% over 12 months5,7), allowing targeted, indicated prevention strategies which are likely to have the greatest effect on outcomes.8–10

Studies using the close-in approach have been referred to as “ultrahigh risk” (UHR) or clinical high-risk studies to differentiate them from traditional genetic high-risk studies that rely on family history as the primary inclusion criterion. The terms “at-risk mental state” or “UHR” do not imply that a full-threshold psychotic illness, such as schizophrenia, is inevitable but suggest that an individual is displaying a “need-for-care” and is at increased risk of developing a psychotic disorder by virtue of his or her mental state. The UHR diagnostic criteria have been articulated and refined by researchers at the University of Melbourne1,5 and Yale University.11 These researchers have developed sets of criteria for identifying UHR individuals based on the presence or onset of one or more of the following criteria: attenuated psychotic symptoms (ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking and speech), brief limited intermittent psychotic symptoms too short in duration to meet Diagnostic and Statistical Manual of Mental Disorder criteria for psychosis (symptoms spontaneously resolved within 1 week) and family history (first degree) of a psychotic or bipolar

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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 neuropathological 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 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 neuropathological studies. Our initial investigations concentrated on the pattern of cortical folding in this region because this is typically established during the early stages of...
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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.\textsuperscript{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.\textsuperscript{41} This pattern represents a loss of the “normal” leftward bias that we previously identified\textsuperscript{42} and is similar to that observed in patients with chronic schizophrenia.\textsuperscript{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.\textsuperscript{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,\textsuperscript{45} and the continuous performance test-identical pairs,\textsuperscript{46} do not show differential impairments in UHR patients depending on psychosis outcome.\textsuperscript{34,47} However, these measures are not especially good indicators of cingulate function,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 UHR-P patients compared with UHR-NP.\textsuperscript{35} Similar (although more posterior) findings have been reported recently in a somewhat smaller sample.\textsuperscript{27} However, one limitation of this work is that significant group differences in ACC GM may be an artifact of variations in cortical folding patterns because variability in local sulcal and gyral anatomy has been shown to influence morphometric estimates in and around the region.\textsuperscript{50,51} Coupled with findings that patients and controls do indeed show different patterns of gyrification in the ACC, any case-control comparisons may be seriously biased unless such folding variations are accounted for. To address this problem, we recently matched UHR individuals to control for morphology of 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 non-schizophreniform (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.\textsuperscript{52} However, our data from 135 UHR patients (39 of whom transitioned to psychosis) reveal no such enlargement prior to the onset of illness.\textsuperscript{53} Similarly, amygdala involvement has been proposed, based on reductions in chronic illness\textsuperscript{52} and its role in emotional processing.\textsuperscript{54} We have reported that amygdala volume is not significantly smaller in UHR patients, with no difference between UHR-P and UHR-NP patients.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 psycho-
sis. Our first study reported significant neuroanatomical
changes over the transition to psychosis in cingulate, me-
dial 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 fron-
tooccipital 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 lim-
itations to both studies, including small numbers, the use
of relatively thick slices that may hinder detection of sub-
tle changes, and the aforementioned problems of brain
registration. We have attempted to deal with these limi-
tations by using a different approach that assesses expan-
sion 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 accelerat-
ed rate of GM retraction in preschizophrenic UHR
individuals during the transition to psychosis. Interes-
tingly, 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 ex-
acerbation of normal neurodevelopmental processes.
Further, the rate of GM retraction was significantly asso-
ciared with proximity to the transition point to psychosis. Such work awaits replication with larger cohorts—in
particular, the addition of a control group and investiga-
tion 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 perfor-
mance. 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 impair-
ments 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)
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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