Brain changes during the onset of schizophrenia: implications for neurodevelopmental theories

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ABSTRACT

- Neuroimaging studies of individuals at risk of psychosis have the potential to identify markers predictive of illness onset and features that progress with transition.
- To date, reduced brain volumes have shown weak predictive value for onset of psychotic illness.
- All published longitudinal studies of the transition to psychosis show progressive brain changes that are not seen in at-risk individuals who do not develop the disorder.
- Although the cause of these changes is unclear, they challenge the conventional neurodevelopmental model of schizophrenia.

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Neuroimaging in longitudinal investigations of individuals who are at increased risk of developing psychosis has provided insight into the period of transition from the at-risk mental state to the illness or psychosis state. Identification of such cohorts has generally been approached in one of two ways, using either clinical or genetic risk factors. The clinical approach focuses on positive symptoms or self-recognised "basic symptoms", resulting in identification of "help-seeking" adolescents and young adults.[1] By definition, these people may already be manifesting signs of attenuated onset of psychosis, as these state-based criteria are thought to identify an at-risk mental state.[2] The genetic approach recruits young people with varying degrees of genetic risk — for example, the Edinburgh High Risk Study's strategy has been to recruit young asymptomatic subjects (aged 16–24 years) who have at least two family members with a confirmed diagnosis of schizophrenia.[3] Both approaches aim to identify neurobiological features that distinguish those people who later develop psychosis (or schizophrenia, depending on the research centre), and discover what, if anything, changes during the transition to illness.

Studies using the clinical approach have been referred to as ultra-high 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" and "ultra-high risk" do not imply that a full-threshold psychotic illness such as schizophrenia is inevitable; rather, they suggest that an individual is displaying a need for care, and is at increased risk of developing a psychotic disorder by virtue of their mental state.[2] Both the genetic and the clinical high-risk approaches aim to maximise the proportion of recruited participants who develop psychosis over a feasible interval — as high as 30%–40% over 24 months in many studies.[1]

Most neuroimaging studies of people at risk of psychosis have been cross-sectional.[4,5] These aimed to demonstrate that structural changes found in patients with schizophrenia would also be identified before onset, based on the dominant neurodevelopmental theory of the disorder. This traditional model proposes that abnormalities in fetal brain development during early stages of neuronal selection and migration are the principal reasons for failure of brain functions in early adulthood.[6] An array of data — such as an increased rate of obstetric complications, minor physical abnormalities, neurological soft signs, and subtle behavioural abnormalities in children who later develop schizophrenia — support the importance of neurodevelopmental factors in the pathogenesis of schizophrenia in particular, but probably also do so for a range of neuropsychiatric disorders in general. Furthermore, the prevalence of these risk factors in the non-affected population is substantial, and their positive predictive value for the development of schizophrenia is limited. This last point has been borne out in imaging studies of at-risk individuals, with reduced brain volumes showing "little more than weak predictive utility"[5] for future onset of psychotic illness, despite consistent findings of volumetric reductions in established schizophrenia.[7] The most promising findings to date concern reductions in right prefrontal grey matter volume (including the right insula), which have been found in two voxel-based morphometry (VBM) studies of UHR individuals.[8,9] Patients in the Edinburgh High Risk Study who later developed schizophrenia also had smaller right prefrontal grey matter volume.[10] However, it is yet to be demonstrated that volumetric differences in this or any other region can reliably predict onset.[4,5]

A possible explanation for these findings is that the early stages of schizophrenia are associated with variable pathological changes in several brain structures, which can only be tested by longitudinal studies of schizophrenia onset. We previously reported data from 21 UHR individuals who had a baseline magnetic resonance imaging (MRI) scan and were followed up with a second MRI scan, either immediately after psychosis or after at least 12 months had elapsed for those who did not develop psychosis. Significant neuroanatomical changes during the transition to psychosis were identified in cingulate, medial temporal and orbitofrontal regions, using VBM.[9] Although these changes were not found in UHR individuals who did not develop psychosis between the two scans, the group-by-time interaction term was not significant. In a similar VBM study of white matter, we found that patients who develop psychosis show reductions in deep left parietal white matter near the fronto-occipital fasciculus and in left occipital white matter subadjacent to the calcarine cortex, as well as bilateral increases in the posterior cerebellum.[11]

These findings have been largely supported by a subsequent VBM follow-up study of genetic high-risk individuals, which examined brain changes over 2 years in 65 young, high-risk adults compared with 19 healthy controls.[12] The high-risk group exhibited significant reductions in grey matter density in the temporal lobes and the right frontal and right parietal lobes, which were not observed in the healthy group. Comparison of individuals with transient or isolated psychotic symptoms ($n=18$) with those without such symptoms showed progressive changes in left temporal lobe regions, including the hippocampus. Eight of the high-risk individuals who later developed schizophrenia (three at the time of the second scan, five after the second scan) showed

reductions in the left inferior temporal lobe, left uncus and right cerebellum. These findings are interesting as they suggest that detectable brain changes may occur up to 2 years before the frank onset of schizophrenia. Importantly, the subjects were all neuroleptic-naïve, indicating that medication did not explain these changes.

However, there are several methodological limitations to the above three studies, including small participant numbers, use of relatively thick image slices that could hinder detection of subtle changes, and failure to deal with errors in brain registration between individuals with variations in cortical folding.[13] We have attempted to deal with some of 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. Using a slightly larger (but overlapping) population of UHR individuals than in our earlier study, these more sensitive analyses were able to show significantly greater brain contraction in the right prefrontal region specific to participants who developed psychosis, indicative of an accelerated rate of grey matter retraction in pre-psychotic UHR individuals during transition to psychosis.[14] Interestingly, the pattern of longitudinal change seen in the group who developed psychosis 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.[15] Furthermore, the rate of grey matter retraction was significantly associated with proximity to the transition point to psychosis. This work needs to be replicated with larger cohorts, and the addition of a control group and investigation of possible medication-related effects would be important advances.

Despite the advances made using this surface-based method, it was not possible to examine the medial brain surface or cortical regions in deep sulci such as Heschl's gyrus. We recently completed a manual tracing study in the same population to investigate changes in the superior temporal gyrus (STG) during the transition period, with an average time between scans of about 18 months. Bilateral reductions of about 5% per year (± 5%) were found in those who developed psychosis, and these were significantly greater than those seen in the controls and non-psychotic UHR groups, which both showed no change on average.[16] Although the losses in those who developed psychosis are large, they are unlikely to continue for the entire illness — indeed, our own data suggest that the reductions in first-episode psychosis are smaller (2% to 3% per year).[16] Abnormalities of the STG have been repeatedly described in schizophrenia,[7] and reductions in volume (especially on the left) are associated with auditory hallucinations and thought disorder,[17,18] suggesting that these progressive changes might explain the increase in symptoms that characterise the transition to psychosis.

The cause of these progressive changes is unclear. There are a number of possibilities, including brain changes that result from changes in physical activity,[19] and altered cognition around the time of transition.[20] A possibility that we have investigated is stress around the time of illness onset and an associated disturbance of hypothalamic–pituitary–adrenal (HPA) axis function.[21] There is good evidence of an association between stress hormones, such as cortisol, and structural damage to medial temporal regions.[22] In recent preliminary analyses of a small sample of UHR individuals, we identified that cortisol levels were associated with level of depression and anxiety, but not psychotic symptoms.[23] An alternative, indirect index of HPA axis dysfunction can be obtained by examining pituitary volumes on MRI scans.[24] We measured the pituitary volume in 94 UHR individuals (selected from our larger sample to exclude the effects of medication) and 49 control participants. UHR individuals who later developed psychosis had pituitaries that were, on average, 12% larger than those in UHR-participants who did not develop psychosis. Furthermore, the risk of developing psychosis during the follow-up period increased by 20% for every 10% increase in baseline pituitary volume. This suggests that abnormal HPA axis function around the time of transition to psychosis and during its earliest phases might drive some of the brain changes seen in prefrontal and medial temporal regions. Additional longitudinal studies and investigations assessing the impact of stress and other aetiological factors around the time of illness onset are needed to understand the mechanisms that underlie changes in brain structure. Some of these are underway, including studies from our group that are assessing limbic and other cortical regions in detail.

Confounding factors could also result in progressive brain change, the two most obvious being antipsychotic medication and illicit drug use (particularly cannabis). There is evidence for excessive brain loss over time in cannabis-using patients with first-episode schizophrenia compared with non-using patients,[25] but the differences are subtle. In addition, cannabis use per se has not been found to predict onset of psychosis in a clinical high-risk group.[26] However, this does not exclude the possibility of an interaction between cannabis use and the process that underlies the transition leading to brain changes.

Evidence for an effect of antipsychotic medication is also uncertain. Animal studies have demonstrated that both typical and atypical antipsychotics increase neurone density[27] and decrease brain volume.[28] However, studies of humans with schizophrenia show cortical expansion,[29] contraction[30] and no change[31,32] after treatment with antipsychotics, as well as evidence that the potential effects of medication are significantly less than the effects of the disorder.[33] Furthermore, brain changes have been reported to occur before any medication was prescribed,[12] and changes detected in our studies occurred with minimal exposure to antipsychotics.[9,14,34]

Summary and conclusions

Although longitudinal studies of schizophrenia in at-risk individuals show promise, few have been conducted, and these do not demonstrate consistent neuroimaging changes during the transition to psychosis. In addition, they raise questions regarding exactly when the changes in brain structure and function occur with respect to the development of psychopathological symptoms. Despite this, measures of change over time have been shown to improve the prediction of schizophrenia.[35] Furthermore, every longitudinal imaging study of high-risk groups has challenged the prevailing models of schizophrenia[36] and supported the growing evidence for progressive brain changes after onset of the disorder.[37] The initial results suggest excessive brain changes consistent with the clinical changes seen in these individuals as they develop frank psychosis.

We have suggested that several processes could underlie the observed abnormalities and dynamic changes in early psychosis.[36] In particular, progressive changes around the time of transition to illness might be related to both the effects of stress hormones and alterations of the normal maturational processes (eg, increased

myelination, synaptic proliferation and pruning, and subtle loss of grey matter volume).[38] Further studies are required to establish the veracity of this proposal, as well as the degree of interaction between these processes and genetic and social environments.

If active brain changes occur as the illness emerges, these could be prevented, ameliorated or at least delayed by early intervention — for example, to reduce the impact of stress and stress-related hormones.[21] Preliminary studies suggest that intervention at this early stage may reduce transition to psychosis;[39] these data need to be replicated with larger numbers of participants.

Perhaps unsurprisingly, all the currently available longitudinal studies report volumetric analyses only. Other modalities are likely to provide additional data — for example, brain spectroscopy has the potential to detect differences in brain metabolites, including neurotransmitters such as glutamate and GABA, which might show changes during transition. However, there is a large range of normal physiological variation, so the capacity for detecting subtle changes may be limited.[40,41] The most promising technique is functional MRI, as it examines neurobiology and cognition, although to date there have been no longitudinal studies of at-risk individuals, and it is still unclear whether assessment of an activation/deactivation paradigm or a resting state will be most useful. The combination of functional imaging with spectroscopy has been informative in other disorders, such as addiction.[42] Incorporation of additional modalities and analysis methods (eg, diffusion tensor imaging and machine learning analysis) is likely to improve our understanding of the onset phase of schizophrenia.

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Competing interests

None identified.

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