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Structural Brain Alterations in Individuals at Ultra-high Risk for Psychosis: A Review of Magnetic Resonance Imaging Studies and Future Directions

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Individuals at ultra-high-risk (UHR) for psychosis have become a major focus for research designed to explore markers for early detection of and clinical intervention in schizophrenia. In particular, structural magnetic resonance imaging studies in UHR individuals have provided important insight into the neurobiological basis of psychosis and have shown the brain changes associated with clinical risk factors. In this review, we describe the structural brain abnormalities in magnetic resonance images in UHR individuals. The current accumulated data demonstrate that abnormalities in the prefrontal and temporal cortex and anterior cingulate cortex occur before illness onset. These regions are compatible with the regions of structural deficits found in schizophrenia and first-episode patients. In addition, the burgeoning evidence suggests that such structural abnormalities are potential markers for the transition to psychosis. However, most findings to date are limited because they are from cross-sectional rather than longitudinal studies. Recently, researchers have emphasized neurodevelopmental considerations with respect to brain structural alterations in UHR individuals. Future studies should be conducted to characterize the differences in the brain developmental trajectory between UHR individuals and healthy controls using a longitudinal design. These new studies should contribute to early detection and management as well as provide more predictive markers of later psychosis.

Key Words: Schizophrenia; Ultra-high-risk; Magnetic Resonance Imaging; Psychotic Disorders; Neurodevelopment; Predictive Marker

INTRODUCTION

Neuroimaging research has consolidated its position as the major approach to investigate the human brain in vivo and has contributed to the improvement of knowledge about the biological basis of psychosis, especially schizophrenia. Schizophrenia is generally accepted as a neurodevelopmental disorder in which the most consistent morphological findings are enlarged lateral ventricles and reduced volume in the prefrontal and medial temporal lobes (1, 2). Although these abnormalities are evident in schizophrenia patients, the timing of their occurrence remains unclear. Advances in neuroimaging technologies and a ultra-high-risk (UHR) strategy that uses clinical-state-based criteria for identifying prodromal individuals, has resulted in renewed interest in brain development associated with the course of schizophrenia because the advances in research provide important insight into how brain changes occur (3). This strategy is a promising approach for the investigation of the neurobiological basis of risk for and conversion to illness that might provide potential prodromal markers of psychosis. Many neuroimaging studies in UHR individuals have reported alterations in several brain regions that correspond to structural abnormalities found in schizophrenia, particularly the frontal and medial temporal cortices, anterior cingulate cortex (ACC), and superior temporal gyrus (STG) (4-6). Several hypotheses based on evidence about such brain abnormalities in UHR individuals have been proposed. Such deficits precede the onset of illness and certain events such as an intense or prolonged stressor or other environmental factors might exacerbate these deficits. Alternatively, such deficits could mark the onset of illness (5, 6).

In this paper, we review the recent literature on brain magnetic resonance imaging (MRI) changes in individuals at UHR for psychosis. Previous structural MRI studies in individuals at UHR are summarized in Table 1. We discuss the work of other groups as well as our own efforts. We have recently reported cross-sectional cognitive and neuroimaging studies as well as

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Table 1. Structural imaging studies in ultra-high-risk subjects

Author	Year	Subjects	Conversion† and Follow-up‡	Measure	Main findings
Region of interest (ROI)					
Phillips et al.	2002	60 UHR 32 FEP 139 HC	20 UHR-P 40 UHR-NP	Hippocampus and whole brain volumes	Smaller bilateral hippocampus in UHR compared to HC Increased L hippocampus in UHR-P compared to UHR-NP and FEP
Yücel et al.	2003	63 UHR 75 HC	21 UHR-P 42 UHR-NP	ACC morphology	More interrupted left cingulate sulcus and paracingulate sulcus in UHR No differences between UHR-P and UHR-NP
Garner et al.	2005	94 UHR 49 HC	31 UHR-P 63 UHR-NP	Pituitary volume	Increased pituitary volume in UHR-P compared to UHR-NP Decreased pituitary volume in UHR-NP compared to UHR-P or HC
Wood et al.	2005	79 UHR (35 UHR+ 44 UHR-) 49 HC	24 UHR-P	Hippocampus volume ACC morphology	Smaller left hippocampal volume in UHR- than UHR+ Similar pattern of L ACC and trend level difference of reduced PCS folding and more frequent CS interruptions in UHR- and UHR+
Velakoulis et al.	2006	135 UHR 89 SZ 162 FEP 87 HC	39 UHR-P 96 UHR-NP	Hippocampus, amygdala and whole brain volumes	Whole brain volume reduction in UHR No differences in hippocampus and amygdala volume between UHR-P and UHR-NP
Hurlemann et al.	2008	36 UHR (20 EPS 16 LPS) 36 HC	3 EPS 5 LPS	Hippocampus volume and Rey auditory verbal learning test	Bilateral reduced hippocampal volumes in both EPS and LPS
Takahashi et al.	2008	135 UHR 162 FEP 89 SZ 87 HC	39 UHR-P 96 UHR-NP	AI length and prevalence	Shorter AI in UHR, FEP and SZ than HC No difference between UHR-P and UHR-NP
Takahashi et al.	2008	135 UHR 162 FEP 89 SZ 87 HC	39 UHR-P 96 UHR-NP	CSP length and large CSP prevalence ACC surface morphology	No difference between the groups No difference between UHR-P and UHR-NP No difference between UHR+ and UHR- No effects of CSP length on ACC sulcal features
Choi et al.	2008	30 UHR 23 GHR 34 HC	4 UHR-P	CSP length and larger CSP prevalence	Higher abnormal CSP in UHR than HC
Takahashi et al.*	2009	97 UHR 55 HC	31 UHR-P 66 UHR-NP 51 rescanned (11 UHR-P 20 UHR-NP 20 HC)	Insular volume	In cross-sectional comparison: Smaller insular volumes in UHR-P bilaterally compared with UHR-NP and with HC on R hemisphere In longitudinal comparison: Greater reduction in bilateral insular volumes in UHR-P than UHR-NP or HC
Takahashi et al.*	2009	35 UHR 23 FEP 22 HC	12 UHR-P 23 UHR-NP	STG and its subregion volumes	In cross-sectional comparison: Smaller planum temporal in male UHR-P than HC at follow-up In longitudinal comparison: Reduction in planum polare, planum temporal, and caudal region in UHR-P and FEP compared with HC and/or UHR-NP
Buehlmann et al.	2010	37 UHR 23 FEP 22 HC	16 UHR-P 21 UHR-NP	Hippocampus volume	Smaller L hippocampus in FEP than UHR or HC Larger L hippocampus volume in UHR-P than FEP but no HC No-significant trend in left hippocampus among UHR-P, UHR-NP, FEP, and HC No difference between UHR-P and UHR-NP
Witthaus et al.	2010	29 UHR 23 FEP 29 HC	8 UHR-P	Hippocampus and amygdala volumes	Smaller volumes of bilateral hippocampus corpus and tail in UHR than HC Smaller R hippocampus corpus and tail in UHR-P than UHR-NP Smaller L amygdala volumes in FEP than UHR or HC
Takahashi et al.	2010	97 UHR 42 HC	31 UHR-P 66 UHR-NP	STG and its subregion volumes	Smaller bilateral STG in UHR at baseline than HC No difference between UHR-P and UHR-NP
Wood et al.	2010	66 UHR 29 HC	7 UHR-P 59 UHR-NP	Hippocampus volume and T2 relaxation time	Smaller L hippocampal volumes in both UHR-P and UHR-NP than HC Smaller R hippocampal volume in UHR-NP than HC
Voxel based morphometry (VBM)					
Pantelis et al.*	2003	75 UHR	23 UHR-P 52 UHR-NP 21 rescanned (10 UHR-P 11 UHR-NP)	VBM	In cross-sectional comparison: Reduction in R medial and lateral temporal and inferior frontal cortex, and bilateral cingulate UHR-P compared UHR-NP In longitudinal comparison: Reduction in L parahippocampal, fusiform, cingulate and cerebellar cortices, and OFC in UHR-P

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Table 1. *(continued from the previous page)* Structural imaging studies in ultra-high-risk subjects

Author	Year	Subjects	Conversion† and Follow-up‡	Measure	Main findings
Borgwardt et al.	2007	35 UHR 25 FEP 22 HC	12 UHR-P 23 UHR-NP	VBM using SPM2 and x-BAMM	Reduction in L cerebellum in UHR-NP Difference in L insula, STG, ACC and precuneus between 3 groups Reduced volume in L medial temporal cortex in UHR compared to HC Reduction in R insula, inferior frontal and STG in UHR-P compared to UHR-NP
Borgwardt et al.	2007	12 UHR-P 25 FEP 22 HC	25 months	VBM using SPM2 and x-BAMM	Smaller bilateral PCC, precuneus, paracentral lobule, and L superior parietal lobule and greater L parietal/posterior temporal region in UHR-P than HC Greater bilateral temporal gyrus and smaller R lentiform nucleus volumes in UHR-P than FEP
Meisenzahl et al.	2008	40 UHR 75 HC	15 UHR-P 25 UHR-NP	VBM using SPM5	Reduced volumes in frontal, lateral temporal and medial temporal regions in UHR compared to HC Inverse correlations between prefrontal gray matter volume and PANSS scores
Borgwardt et al.*	2008	20 UHR	20 rescanned (10 UHR-P 10 UHR-NP)	VBM using SPM5	Longitudinal volume reductions in OFC, superior frontal, inferior temporal, medial and superior parietal cortex, and cerebellum in UHR-P No longitudinal changes in UHR-NP
Ziermans et al.	2009	54 UHR 54 HC	7 UHR-P	VBM	No difference between UHR and HC
Koutsouleris et al.	2009	46 UHR (20 EPS, 26 LPS) 75 HC	15 UHR-P (1 EPS, 14 LPS) 18 UHR-NP	VBM using SPM5	Reduced volume in fronto-temporo-limbic structures in LPS compared with HC Bilateral temporolimbic alterations and subtle prefrontal abnormalities in EPS Prefrontal abnormalities in UHR-P compared with UHR-NP and with HC
Witthaus et al.	2009	30 UHR 23 FEP 29 HC	1 UHR-P	VBM using SPM2	Reduced volume in bilateral cingulate gyrus and hippocampus, R inferior frontal and STG in UHR compare to HC Smaller volume in bilateral cingulate cortex and hippocampus, L parahippocampus, OFC, amygdala and fusiform gyrus, R STG, inferior frontal and temporal pole in FEP than UHR
Visual inspection					
Borgwardt et al.	2006	37 UHR 30 FEP 17 DC 26 HC		Blinded MRI scans assessment by a radiologist	Higher radiological findings in UHR and FEP than DC or HC Higher prevalence of large CSP in UHR No difference between UHR and FEP
Surface based method					
Fornito et al.	2008	70 UHR 33 HC	35 UHR-P 35 UHR-NP	ACC morphometry	Reduced thickness of a rostral paralimbic ACC region in UHR-P compared to HC Increased thickness in dorsal and rostral limbic areas in UHR-NP compared to HC
Sun et al.*	2009	35 UHR	35 rescanned (12 UHR-P 23 UHR-NP)	Cortical pattern matching	Greater brain surface contraction in R prefrontal region in UHR-P than UHR-NP Non-significant trend in L prefrontal region and bilateral occipital region in UHR-P
Jung et al.	2010	29 UHR- 29 HC 31 SZ	8 UHR-P 21 UHR-NP	Surface-based cortical thickness	Cortical thinning in STG, MTG, PFC, parietal cortex, ACC, parahippocampal cortex in UHR compared with HC
Group detection using cortical gray matter differences					
Haller et al.	2009	20 UHR 20 FEP 20 HC		Cortical thickness analysis and cortical thickness asymmetry	No difference in direct cortical thickness Cortical thickness asymmetry in frontal, temporal and parietal regions help distinguish between UHR and HC
Koutsouleris et al.	2009	20 EPS 25 LPS 25 HC	15 UHR-P 18 UHR-NP	Multivariate neuroanatomical pattern classification using SVM	High classification accuracy between EPS, LPS and HC High classification accuracy between UHR-P, UHR-NP, and HC UHR-P vs. HC & UHR-P vs. HC: ACC, PCC, OFC, LPFC, LTG, medial TG, caudate UHR-P vs. UHR-NP: medial & LTG, LPFC, thalamus, cerebellum

*indicates longitudinal MRI study; †indicates psychosis conversion rate during clinical follow-up; ‡indicates sample size involved in MR follow-up.
UHR, ultra-high-risk subjects; FEP, first-episodic patients; HC, healthy controls; SZ, schizophrenia patients; UHR-P, those who convert to psychosis; UHR-NP, those who did not convert to psychosis; UHR+, UHR subjects with family history of psychosis; UHR-, UHR subjects without family history of psychosis; EPS, UHR subjects in early prodromal states; LPS, UHR subjects in late prodromal states; GHR, genetic-high-risk subjects; DC, depressive controls; L, left; R, right; PANSS, the Positive and Negative Syndrome Scale; VBM, voxel based morphometry; x-BAMM, Brain Activation and Morphological Mapping software; SPM, Statistical Parametric Mapping soft ware; SVM, support vector machine; ACC, anterior cingulate cortex; AI, adhesion interthalamica; CSP, cavum septum pellucidum; CS, cingualte sulcus; OFC, orbitofrontal cortex; PCS, paracingulate sulcus; PCC, posterior cingulate cortex; MTG, middle temporal gyrus; STG, superior temporal gyrus.

conducted longitudinal observations to examine clinical and brain changes in UHR individuals. Throughout this review, we first discuss the most consistent findings in UHR individuals and then examine brain structural alterations as illness-onset markers, followed by suggestions for future directions of neuroimaging studies in UHR individuals.

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BRAIN REGIONS SHOWING STRUCTURAL CHANGES IN UHR INDIVIDUALS

Medial temporal cortex

Accumulative studies of morphological changes in UHR individuals have used diverse methods to measure and identify the MRI features of brain structures, such as manual and automated region of interest (ROIs), voxel-based morphometry (VBM), and surface-based cortical thickness methods. The manual ROI method is considered the gold standard of 3D quantitative measurements due to its precision and is often used to detect subtle morphological changes. However, because it is time consuming and is specific to particular brain regions, most ROI studies to date in UHR individuals have focused on the medial temporal cortex, including the hippocampus, which is one of the key regions in the neuropathology of schizophrenia (4, 6). ROI studies of hippocampal volume have frequently reported smaller volumes in UHR individuals than in healthy controls, particularly in the left hemisphere (7-9), although these findings have been inconsistent (10). Such abnormalities in the left hippocampus have also been reported in first-episode patients (FEPs) (10, 11). Findings from VBM studies in UHR individuals that have shown reduced gray matter in the hippocampus and adjacent parahippocampal cortex (12, 13) are compatible with those from ROI approaches. Neurocognitive studies in UHR individuals have reported memory impairment, which is sensitive to hippocampal damage (14). The left hippocampus is known to subserve verbal memory and suggests that verbal episodic memory is a potential marker of risk for psychosis. This has been supported by several studies with relatively large samples of UHR individuals that have shown significantly poorer memory functions in UHR patients who later converted to psychosis (14-16). In this regard, one study examined whether interrelated structural–functional deficits of the hippocampus are present across early prodromal states (EPSs) and late prodromal states (LPSs) of schizophrenia compared with healthy controls using a combined hippocampal volume and neuropsychological measures (Rey Auditory Verbal Learning Test) (17). Both the EPS and LPS groups have reduced bilateral hippocampus volumes, but these reductions were correlated with a poorer cognitive test performance in only the LPS group. These previous studies suggested a progressive and interrelated structural–functional pathology of the hippocampus as an index of increased risk for psychosis.

Differences in hippocampal volume between UHR patients who later converted to psychosis (UHR-P) and those who did not (UHR-NP) have been investigated by cross-sectional comparison, although the findings from these studies have shown contradictory results. Phillips et al. (18) reported reduced bilateral hippocampal volumes in UHR individuals and FEPs compared with healthy controls. In addition, UHR-P individuals were found to have a greater volume in the left hippocampus at the baseline compared with UHR-NP individuals and FEPs. However, in contrast, a study by the same research group using a larger sample found no significant differences in the hippocampal volume between UHR-P and UHR-NP individuals (10). Buehlmann et al. (7) also reported no significant differences in the hippocampal volume between UHR-P and UHR-NP individuals. However, they found a smaller left hippocampal volume in FEPs than in UHR individuals as well as healthy controls and a larger left hippocampal volume in UHR-P individuals compared with FEPs. Recently, Witthaus et al. (19) divided the hippocampus into two regions, the head and corpus/tail, and compared the volumes of these two subregions in UHR individuals, FEPs, and healthy controls. UHR individuals had a smaller volume in the bilateral hippocampus corpus and tail, but not the head, than the healthy controls. In addition, UHR-P individuals had a reduced volume in the right hippocampus corpus and tail compared with UHR-NP individuals.

Wood et al. (9) investigated the contributions of family history to hippocampal volume in UHR individuals. Those without a family history of psychosis were found to have a smaller hippocampal volume than those with a family history of psychosis. This suggests that morphological anomalies in the hippocampus are affected more by nonspecific environmental factors than by genetic factors. Magnetic resonance spectroscopy (MRS) studies have been conducted to investigate whether metabolic changes are found in the hippocampus of UHR individuals. MRS studies have indicated normal levels of N-acetylaspartate (NAA; a marker of neuronal/axonal integrity) in the hippocampus of UHR individuals (8, 20, 21). Recently, Wood et al. (8) investigated hippocampal volume and MRS as well as hippocampal T2 relaxation time, which is highly sensitive to the presence of neuropathological changes. The UHR-P group had a significantly elevated T2 relaxation time for the left hippocampal head. These findings suggest that morphological anomalies in the hippocampus occur before the onset of psychosis, but are not related to transition, and the magnitude of reduced hippocampal volume matches the stage of illness (11, 13), although the study with the largest sample did not support this conclusion (10).

Superior temporal gyrus

The STG is also one of the key regions often investigated by the ROI approach in schizophrenia (22, 23) and UHR individuals (24, 25). Several studies in schizophrenia and FEPs have reported a reduced volume in the STG, particularly in the left hemisphere, as with hippocampal deficits (1, 22, 26, 27). Volume reduction of the STG in psychosis patients is related to functional deficits, including auditory hallucinations and thought disorder (28, 29). In a longitudinal study of FEPs, progressive reduction in the left STG volume was highly correlated with progressive neurophys-

iological deficits, especially mismatch negativity (MMN) (30). Recently, we investigated MMN in the auditory cortex of UHR individuals to clarify whether MMN deficits appear before illness onset. The UHR group showed reductions in both the amplitude of MMN and the magnetic counterpart of MMN (MMNm) compared with healthy controls (31). We also found a negative correlation between the left MMNm dipole moment and clinical symptoms, in addition to a smaller right MMNm dipole moment than in healthy controls. We suggest that deficits in the early stage of auditory processing exist before illness onset.

Several cross-sectional VBM studies have reported a smaller STG in UHR individuals than in healthy controls (12, 32, 33). Our recent findings in cortical thickness measurement using a surface-based method are consistent with previous VBM findings that have shown a decreased left STG cortical thickness in UHR individuals compared with healthy controls (34). In particular, the mean cortical thickness in the STG gradually decreases according to psychotic stages (i.e., in order, healthy controls, UHR individuals, and schizophrenia patients). Recently, Takahashi et al. (24) conducted a longitudinal examination of the STG subregions (planum polare, Heschl's gyrus, planum temporale, and rostral and caudal regions) in UHR individuals. In cross-sectional comparisons, they found no differences in the whole STG and its subregions at the baseline between UHR individuals and healthy controls as well as no differences between UHR-P and UHR-NP individuals, whereas male UHR-P individuals had a smaller planum temporale at follow-up than did the healthy controls. In longitudinal comparisons, UHR-P individuals showed a significant reduction in the planum polare, planum temporal, and caudal regions of the STG compared with UHR-NP individuals and healthy controls. A more recent study from the same center with a larger sample of antipsychotic-naïve individuals at UHR reported smaller bilateral STG volumes at the baseline in UHR patients compared with healthy controls, but no differences between UHR-P and UHR-NP individuals (25).

Speculatively, abnormalities of the STG in schizophrenia might be associated with deficits in face perception often noted in schizophrenia patients because the STG and fusiform gyrus play central roles in processing faces (35). Our group recently reported specific problems in configural face processing in schizophrenia and suggested that inadequate facial recognition in schizophrenia results from deficits in processing configuration information (36). More recently, we also found deficits in the processing of facial configuration in UHR individuals suggesting that the deficits contribute to social dysfunction in schizophrenia (37). Deficits in social functioning in UHR individuals have been assessed using the Social Functioning Scale (38).

Taken together, findings from other centers and our own group suggest that UHR individuals have structural and functional abnormalities in the STG before illness onset, particularly in the left hemisphere. In addition, it is suggested that a progressive regional pathological process in the STG occurs before the first expression of frank psychosis, and such deficits might lead to deficits in social functioning.

Frontal cortex

Structural abnormalities in several frontal regions have been reported in UHR individuals, particularly in the prefrontal cortex (PFC), including the dorsolateral PFC (DLPFC), medial PFC (MPFC), and the ACC. Reduced PFC gray matter has been consistently reported by our group and others (34, 39). Recent MRS studies have reported deficits in the prefrontal metabolic state in UHR individuals. One study found a significant elevation of the NAA/creatine and choline/creatine ratios in the left DLPFC in UHR individuals, which was interpreted as a decline in creatine indicative of hypometabolism (21), whereas another study showed a significant reduction in the NAA/creatine and NAA/choline ratios in the left frontal lobe (40). However, our recent MRS study found no differences in the left DLPFC between UHR subjects and healthy controls (41). The discrepancies in these findings might partly have arisen from differences in sample characteristics such as age and definition of volumes of interest. Deficits in the PFC in UHR individuals might be related to cognitive dysfunction, such as working memory and attention deficits (4, 15). In particular, spatial working memory ability has been suggested as a marker of risk for psychosis (42). In this context, we recently conducted a study in which UHR individuals performed a spatial working memory task during functional MRI scanning. Our data showed decreased DLPFC activation in UHR individuals compared with healthy controls (Choi et al. in preparation).

Abnormalities in the midline cortical structures that include the MPFC and ACC have been reported (34). We recently found impaired social cognition, such as theory of mind, in UHR individuals (43). This could be the result of reduced gray matter in the MPFC, which plays a role in social cognition. A recent review suggested that alterations in cortical midline structures during the prodrome might be related to phenomenological disturbances, particularly a disrupted sense of self, based on the involvement of the MPFC and ACC regions in self-related processing (44). The recently discovered default mode network (DMN) is a set of brain regions that mainly consists of the MPFC and the posterior cingulate cortex that are involved in self-referential processing (45). Thus, it is valuable to examine whether abnormalities in the DMN exist in the UHR group. Therefore, we reconstructed and compared the intrinsic organized DMN of the resting brain in UHR subjects and healthy controls based on functional MRI time series correlation. Our data showed that compared to healthy controls, UHR subjects showed hyperconnectivity within the default network regions (46).

Abnormalities of the ACC region have been implicated in the pathophysiology of psychotic disorders (47). This region is as-

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sociated with impaired cognition, such as self-monitoring and disorganization in schizophrenia patients (48). The pattern of cortical folding in this region has been investigated in UHR individuals because of the evidence for early neurodevelopmental anomalies. UHR individuals have a poorly developed left paracingulate sulcus and an interrupted left cingulate sulcus compared with healthy controls (49). Wood et al. (9) examined the contribution of a family history of schizophrenia to ACC morphology and found that UHR individuals without a family history of schizophrenia had reduced paracingulate folding and more frequent cingulate sulcus interruptions in the left hemisphere compared with UHR individuals with such history, although this difference was not significant. These authors suggested that these morphological abnormalities in the ACC are related more to environmental factors than genetic factors (9). Several VBM studies have reported decreased ACC gray matter volume in UHR individuals compared with healthy controls (12, 33). Our cortical thickness study also found a decreased ACC thickness in UHR individuals compared with healthy controls (34). Recently, Fornito et al. (50) suggested that ACC abnormalities precede psychosis onset based on a cortical surface-based protocol for parcellating the ACC. An MRS study found a lower NAA/creatine ratio in the ACC in UHR individuals (40), but our group found no significant differences in any metabolite between UHR individuals and healthy controls (41).

Other brain regions

Structural alterations in other brain regions have been reported in UHR individuals compared with healthy controls. Abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis have been suggested in UHR individuals based on HPA-axis hyperactivity in FEPs and psychotic patients (51, 52). Garner et al. (53) found that a larger pituitary volume is associated with the future development of psychosis that suggests an increase in the activation of the hormonal stress response. Thompson et al. (54) provided evidence for HPA-axis dysfunction in UHR individuals by examining the relationships between cortisol and glucocorticoid receptor numbers and pituitary volume.

Morphological abnormalities in limbic system regions such as the insular cortex and the amygdala have been suggested in UHR individuals owing to the role of these structures in emotional processing and previous findings of deficits in such processing in schizophrenia patients (10, 19, 55). An ROI study indicated that insular cortex abnormalities precede the first expression of frank psychosis and progressive pathological changes occur in the insular cortex during the transition period (55). However, ROI studies of amygdala volume have not found significant differences between UHR individuals and healthy controls (10, 19).

Some studies have investigated the brain structures of UHR individuals, particularly the midline structures of the brain such as the cavum septum pellucidum (CSP) and adhesio interthalamica (AI), in light of the early neurodevelopmental anomalies. Abnormalities of the CSP, unlike subtle morphological changes in other brain regions, can be detected by visual inspection, and a high prevalence of radiological findings such as the CSP were reported in UHR subjects compared with healthy controls (56). Our first MRI study in UHR subjects investigated the frequency and severity of an enlarged CSP in UHR individuals compared to first-degree relatives of patients with schizophrenia and healthy controls, which is one of the consistent findings in schizophrenia studies (1, 58), according to a grading system (57). Based on the grading scale, we found a significantly higher prevalence of abnormally enlarged CSP in UHR individuals, but not in first-degree relatives of patients with schizophrenia, compared with healthy controls. However, based on CSP length, a study by Takahashi et al. (59) with a large sample (n=135) found no significant differences in the prevalence of an abnormally large CSP between the groups. Takahashi et al. (60) also measured the length and prevalence of the AI in the same sample. They found a shorter AI in UHR individuals than in healthy controls, but no difference between UHR-P and UHR-NP individuals.

BRAIN STRUCTURAL ALTERATIONS AS ILLNESS-ONSET MARKERS

A number of structural MRI studies in UHR individuals have suggested specific brain regions as potential predictive markers of illness onset based on structural differences between the brains of UHR-P and UHR-NP subjects. Manual and automated ROI approaches have found a smaller volume in the hippocampus (18) and insula (55), larger pituitary volume (53), and reduced thickness of the rostral limbic ACC in UHR-P (50) compared with UHR-NP individuals. However, several studies have found no differences in the hippocampus (7, 9, 10), ACC, and amygdala volume (10) between UHR-P and UHR-NP individuals. This discrepancy might have been due to methodological differences such as scanning parameters and imaging analysis methods. Alternatively, it might be considered that a certain method is more sensitive to abnormalities of a specific region than other methods (61). A recent review and meta-analysis of published data showed that UHR-P individuals have gray matter abnormalities in the PFC, ACC, insula, and cerebellum before the transition to psychosis, compared with UHR-NP individuals (5). It has been suggested that structural abnormalities in these regions might be the most predictive markers for a later transition to psychosis. In this regard, one recent study distinguished UHR individuals from healthy controls and UHR-P from UHR-NP subjects using a whole-brain classification with a support vector machine (62). UHR-P versus UHR-NP classification relies on a pattern of gray matter volume reductions that involve the temporal and prefrontal cortices, thalamus, and cerebellum. In contrast, another study found no distinction between UHR

and healthy individuals based on the patterns of changes in cortical thickness, whereas it did distinguish UHR from healthy individuals using patterns of cortical thickness asymmetry (63).

Previous studies have provided evidence to support specific structural alterations in UHR individuals as potential markers of the transition to psychosis. However, most studies are limited by their cross-sectional design. The human brain changes continually throughout the trajectory of brain maturation and aging. In particular, the dorsal frontal and parietal lobes undergo dynamic changes between adolescence and adulthood (64, 65). The group defined as UHR is between 15 and 30 yr of age and their brains are changing along a neurodevelopmental trajectory. A recently published review emphasized developmental considerations in the identification of more valid markers of the transition to psychosis (6). Longitudinal studies are needed to ascertain normal or abnormal trajectories of neurodevelopment in UHR individuals. However, only a few studies have investigated the longitudinal changes over the transition to psychosis. To the best of our knowledge, there have been only five longitudinal structural MRI studies conducted on UHR individuals, two whole-brain VBM studies (66, 67), two ROI studies (24, 55), and one whole-brain cortical surface-matching study (39). In the whole-brain VBM approach, Pantelis et al. (66) found progressive reductions in the left orbitofrontal, parahippocampal, fusiform and cingulate cortices, and cerebellum in UHR-P individuals, whereas UHR-NP subjects showed longitudinal reductions in only the cerebellum. Borgwardt et al. (67) reported longitudinal volume reductions in the orbitofrontal, superior frontal, inferior temporal, medial and superior parietal cortices, and cerebellum in UHR-P individuals, whereas they found no longitudinal changes in UHR-NP subjects. The authors suggested that a reduction in gray matter volume in the frontal, temporal, and parietal cortices is particularly associated with psychotic illness, rather than with vulnerability to psychosis. In longitudinal ROI studies, UHR-P individuals showed greater reductions in the insular volume (55) and STG subregions including the planum polare, planum temporale, and caudal region (24) compared with UHR-NP individuals. A longitudinal structural MRI study using cortical pattern matching demonstrated an increasing surface contraction in the right PFC in UHR-P compared with UHR-NP individuals (39). Such a change in the PFC in UHR individuals suggests the involvement of an abnormal neurodevelopmental processes, which is consistent with the acceleration of the normal development that occurs in early-onset schizophrenia (68).

CONCLUSIONS AND FUTURE DIRECTIONS

Over the past two decades, structural MRI studies of UHR individuals have become a major approach to identify the neurobiological basis, underlying risk of, and conversion to schizophrenia. Convergent evidence from structural MRI studies in UHR individuals suggest that abnormalities in the PFC and temporal cortex and the ACC precede illness onset (4). These regions correspond to structural abnormalities found in schizophrenia patients (1) as well as FEPs (69). Regional differences between UHR-P and UHR-NP and longitudinal brain changes, particularly in UHR-P, have led to suggestions that the PFC and temporal cortex may be potential markers of later psychosis (5, 6). What causes structural abnormalities in UHR individuals? Only a few studies have addressed this question by investigating the contributions of genetic factors or of stress to such brain abnormalities (9, 54). An alternative possibility, as discussed above, is that brain abnormalities in UHR individuals might represent an accelerated process of late brain maturation (6). It is still unclear whether inter-individual variation in cortical changes in healthy controls is less than the variation associated with risk of illness (70). During adolescence and early adulthood, the brain undergoes complex and dynamic changes. Cortical changes in each UHR subject could be within the range of normal variation, but those changes show an abnormal developmental trajectory. Given these assumptions and published review articles (5, 6), we could speculate that contradictory findings of previous studies might have resulted from differences in the neurodevelopmental trajectory between samples and that accelerated brain maturation is more predictive than subtle differences in specific brain regions. We suggest that some genes associated with brain development during adolescence and early adulthood affect brain alterations by accelerating the process of normal neurodevelopment (6). Further longitudinal studies should be conducted to characterize the differences in brain developmental trajectory between UHR and healthy individuals. We should also take account of the effects of antipsychotic drugs on brain structures in longitudinal studies of UHR individuals. Structural differences between UHR-P and UHR-NP individuals could influence antipsychotic use in the former group. Therefore, future longitudinal comparisons should be conducted before and after illness onset while subjects are antipsychotic-naïve.

In conclusion, research on UHR individuals is a promising approach for furthering our understanding of the pathophysiology of schizophrenia in the context of neurodevelopment. Structural MRI studies in UHR individuals have contributed to early detection and management as well as suggest predictive neurobiological markers of the transition to psychosis.

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