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Brain structural abnormalities as potential markers for detecting individuals with ultra-high risk for psychosis: A systematic review and meta-analysis

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ABSTRACT

Objective: This study aims to determine whether structural alterations can be used as neuroimaging markers to detect individuals with ultra-high risk (UHR) for psychosis for the diagnosis of schizophrenia and improvement of treatment outcomes.
Methods: Embase and Pubmed databases were searched for related studies in July 2018. The search was performed without restriction on time and regions or languages. A total of 188 articles on voxel-based morphometry (VBM) and 96 articles on cortical thickness were obtained, and another 6 articles were included after the reference lists were checked. Our researchers assessed and extracted the data in accordance with the PRISMA guideline. The data were processed with a seed-based mapping method.
Results: Fourteen VBM and nine cortical thickness studies were finally included in our study. In individuals with UHR, the gray matter volumes in the bilateral median cingulate ($Z = 1.034$), the right fusiform gyrus ($Z = 1.051$), the left superior temporal gyrus ($Z = 1.048$), and the right thalamus ($Z = 1.039$) increased relative to those of healthy controls. By contrast, the gray matter volumes in the right gyrus rectus ($Z = -2.109$), the right superior frontal gyrus ($Z = -2.321$), and the left superior frontal gyrus ($Z = -2.228$) decreased. The robustness of these findings was verified through Jackknife sensitivity analysis, and heterogeneity across studies was low. Typically, cortical thickness alterations were not detected in individuals with UHR.
Conclusions: Structural abnormalities of the thalamocortical circuit may underpin the neurophysiology of psychosis and mark the vulnerability of transition to psychosis in UHR subjects.

1. Introduction

Adolescents and young adults presenting certain subthreshold psychotic symptoms and progressive decline in functioning are considered at "ultra-high risk" (UHR) for psychosis or at risk mental state (ARMS), which possibly progresses into psychosis. The probability of developing psychosis in subjects with clinical high risk is 16% within two years, 18%–36% within three years, and 49% within nine and a half years (Cannon et al., 2007; Klosterkotter et al., 2001; Miller et al., 2002; Tognin et al., 2014; Yung et al., 2008; Yung et al., 2007). Most subjects with UHR do not undergo transition to overt psychosis, but many of them continue to suffer from disruptive psychosocial functioning at follow up (Lin et al., 2011; Nelson et al., 2013; Reniers et al., 2017). Several selection criteria for individuals with UHR include Comprehensive Assessment of At-Risk Mental State (CAARMS) (Smieskova et al., 2010; Yung et al., 2005) and Structured Interview for Prodromal Symptoms (SIPS) (Iwashiro et al., 2016; McGlashan et al., 2001). In general, individuals who present (1) attenuated psychosis symptoms (APS), (2) brief limited psychotic symptoms (BLPS), or (3) reduction in mental state or functioning combined with a genetic risk for psychosis are considered at UHR or at risk mental state (Yung et al., 1998).

An MRI-based morphometric analysis of the brain has been extensively used for investigating neuroanatomical abnormalities in many psychiatric disorders (Hutton et al., 2009). Many studies explored alterations in the gray matter volumes of UHR individuals (Borgwardt et al., 2008; Mechelli et al., 2011; Meisenzahl et al., 2008; Pantelis et al., 2003; Witthaus et al., 2009); however, few studies have investigated cortical thickness (Jung et al., 2011; Schultze-Lutter et al., 2007; Ziermans et al., 2012). Brain volume and cortical thickness reflect the complementary aspects of neuroanatomy and may thus provide valuable

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information for the comprehensive evaluation of the pathophysiological process of schizophrenia. On the one hand, cortical thickness indicates the presence of a specific cortical atrophy. On the other hand, gray matter volume analysis mixes the effect of regional cortical thickness with those of cortical folding and gyrification (Benetti et al., 2013; Hutton et al., 2008). The whole-brain-based morphometrics is a commonly used magnetic resonance image (MRI) analytical approach for investigating cortical gray matter volume and cortical thickness. This method can avoid region of interest (ROI) selection bias and saves more time than the traditional ROI method (Pearlson and Calhoun, 2007). Voxel-based morphometry (VBM) is often used to analyze gray matter volume, and vertex-based morphometry focuses on cortex thickness (Wang et al., 2017).

Owing to the advances in research on neuroanatomy and neuroimaging, a few of the brain structural alterations in the hippocampus, insula, and wide frontal and temporal regions have been consistently reported in patients with schizophrenia and first-episode psychosis (Borgwardt et al., 2008; Ellison-Wright et al., 2008; Honea et al., 2005; Klauser et al., 2015). Given the refractory and chronic illness trajectory and the poor outcome of this disease, early recognition and intervention such individuals have become the major aim of mental health services. An increasing number of researchers have focused on subjects with UHR for psychosis to reduce the risk of developing full-blown psychosis through early clinical psychiatric management. This strategy can be used to explore the underlying neuropathological mechanisms of schizophrenia at the early stage because of the minimal confounding factors of antipsychotic treatment and different illness durations. Cortical abnormalities have been reported in subjects with UHR for psychosis, and several studies have focused on the structure, function, and neurochemistry changes in the brain (Fusar-Poli et al., 2011a; Fusar-Poli et al., 2011b; Fusar-Poli et al., 2007; Smieskova et al., 2010; Wang et al., 2016; Zhu et al., 2019). However, the results are inconsistent. Few studies showed increased or decreased gray matter volume in several brain areas through the ROI approaches or whole-brain morphometrics. By contrast, other works (Iwashiro et al., 2016; Smieskova et al., 2012; Whitford et al., 2012) have negative findings. Similarly, the findings of functional MRI (fMRI) studies on the location and direction of functional alterations are highly heterogeneous. Whether brain structure or function changes before the onset of psychosis and how these alterations develop over time remain unknown. Moreover, determining which alterations in individuals with UHR for psychosis are potential biomarkers for predicting increased susceptibility to psychosis and filling the gap between basic and clinical neuroscience for the clinical diagnosis and treatment of psychosis remain challenging.

The current study reviewed up-to-date structural imaging studies that focused on gray matter volume, thickness alterations, or both of them in UHR subjects to weigh the results of individual studies and determine whether individuals with UHR for psychosis exhibit structural abnormalities in their brain regions before the onset of psychosis. Determining whether these findings are reliable neurobiological markers was also investigated. Meta-analysis of VBM studies was performed with seed-based mapping or signed differential mapping (SDM), a statistical technique for neuroimaging meta-analysis of studies with respect to differences in brain activity or structure. The method was fully validated in several studies. Studies on cortical thickness were systematically studied because of their rarity.

2. Materials and methods

2.1. Study selection

Embase and Pubmed databases were searched for all studies in July 2018 without time limit and restriction to regions or languages. At total of 188 articles about VBM and 96 articles about cortical thickness were obtained. Another 6 articles were obtained after the reference lists were checked. The following MeSH terms and their combinations were searched in [Title/Abstracts]: ultra-high risk/UHR/at risk mental state/ARMS/clinical high risk, schizophrenia/SZ/SCZ/psychosis/psychotic, voxel-based morphometry/VBM/voxel*/morphometry, or cortical thickness. When multiple studies describing the same population were involved, the most comprehensive one was selected.

All the included studies met the following criteria: 1) used VBM to analyze gray matter alterations on whole-brain base; 2) age range of 13–42; and 3) compared UHR subjects with healthy controls (HC) or compared subjects who developed psychosis with those who did not. We excluded 1) peak coordinates that could not be obtained from the article or after contacting the authors; 2) findings based on ROIs; and 3) different thresholds was used throughout the whole brain within one study.

Meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The senior author (Wenbin Guo) resolved any disagreements among authors.

2.2. Data extraction and recorded variables

Data and variables from the included studies were extracted and summarized in tables. We recorded the sample size, gender, and mean age, drug use, study type, assessment instrument and MRI parameters, main findings, statistical threshold, and method employed to correct the results.

2.3. Voxel-based neuroimaging meta-analysis

The extracted data from the involved VBM studies were analyzed through SDM, which is a new method adopting and combining various positive features from previous methods, such as Activation Likelihood Estimation (ALE) or Multilevel Kernel Density Analysis (MKDA). The method was thoroughly described by previous studies (Cooper et al., 2014; Radua et al., 2014). First, the coordinates of the reported cluster peaks were selected for preprocessing with a 10 mm full-width at half-maximum unnormalized Gaussian kernel. Second, statistical and effect-size maps were recreated from those coordinates. Q statistic was calculated to reflect heterogeneity among studies. Specifically, the voxel threshold P of <0.005, peak height threshold SDM-Z of >1.00, and extent threshold of cluster size of ≥ 10 voxels were applied. Finally, the sensitivity of the results was tested through Jackknife analysis. The Egger test and funnel plots reflected the possibility of publication bias. Notably, positive and negative studies were included in the meta-analysis.

3. Results

Fourteen VBM studies with 743 UHR individuals and 588 HC were included in our meta-analysis, and nine cortical thickness studies with 700 UHR subjects and 469 HC were systematically reviewed. Fig. 1 shows the procedures of identifying the studies. Tables 1 and 2 display the demographic data and the detailed technique from these studies involved. Most studies showed no significant differences on age and gender between subjects at UHR for psychosis and controls. The UHR and HC had significant age differences in the studies of Nakamura et al. (2013), Benetti et al. (2013), and Heinze et al. (2015), with HC older than UHR subjects. Similarly, Dukart et al. (2017) observed considerable between-group differences with respect to gender. Only several UHR individuals of these studies had a history of antipsychotic use, whereas the majority of subjects were drug free.

The results of our meta-analysis showed increased gray matter volume in the bilateral median cingulate extending to the paracingulate gyri, right fusiform gyrus, left superior temporal gyrus extending to parahippocampal gyrus, and right thalamus. By contrast, the right gyrus rectus, right superior frontal gyrus, medial part and left superior frontal gyrus, and orbital part showed substantial reduction in gray matter volume (Table 3 and Figs. 2 & 3). The forest plot in Fig. 4 shows the

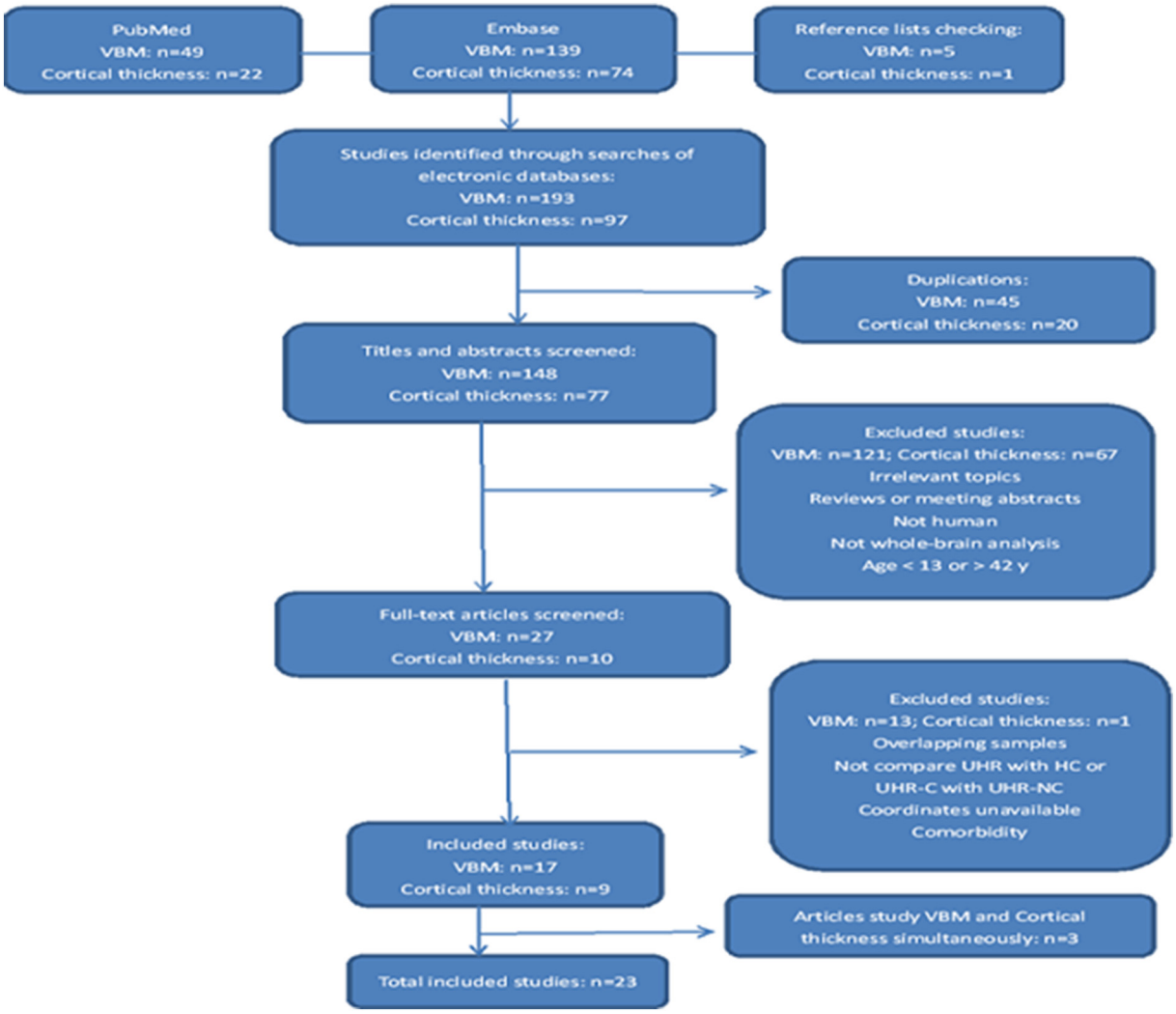


Fig. 1. Selection procedures of voxel-based morphometry studies in subjects at ultra-high-risk for psychosis. Abbreviation: HC, healthy controls; UHR: ultra-high risk; UHR-C: ultra-high risk with subsequent conversion to psychosis group; UHR-NC: ultra-high-risk without subsequent conversion to psychosis group; VBM: voxel-based morphometry; y, years old.

effect size (Cohen's d) of the peak height meta-analysis for the corrected threshold studies.

According to jackknife sensitivity analysis, gray matter volume increased in UHR subjects in the right fusiform gyrus, left superior temporal gyrus, and right thalamus remained significant in all but one combination and in the bilateral median cingulate in all but two combinations. The decreased gray matter volume in the right gyrus rectus and right superior frontal gyrus remained significant in all but one and two combinations, respectively. The result in the left superior frontal gyrus was highly replicable, being preserved throughout all data sets.

For the heterogeneity, the bilateral median cingulate, right fusiform gyrus, and left superior temporal gyrus with increased gray matter volumes showed significant inter-study heterogeneity ($P < 0.005$); whereas the other regions showed no significant between-study heterogeneity.

In the publication bias analysis, the Egger test was significant in the medial part of the right superior frontal gyrus ($P = 0.008$) and the orbital part of the left superior frontal gyrus ($P = 0.001$). Conversely, the results in the other regions were insignificant.

As shown in Table 2, three of the nine involved cortical thickness studies have negative findings ($P < 0.05$). Klauser et al. (2015) found a cluster with increased cortical thickness on the right frontal pole with uncorrected cluster level. Dukart et al. (2017) also found an increased cortical thickness in the parietal and occipital regions. The other four studies and Benetti et al. (2013), Cannon et al. (2015), Dukart et al. (2017), Jung et al. (2011), and Ziermans et al. (2012) demonstrated cortical thinning in the wide frontal, temporal, and occipital areas.

Among these involved studies, five longitudinal studies explored gray matter or cortical thickness differences between those who developed psychosis in the follow-up periods and those who did not. Converters showed an increased gray matter in the right superior, inferior frontal, and Heschl's gyrus than HC. Converters and HC declared no significant differences in one of the three longitudinal cortical thickness studies. By contrast, another two cortical thickness studies showed a reduced cortical thickness in the right superior, middle, and medial orbital frontal gyrus and left angular gyrus, precuneus, and temporo-parieto-occipital regions in converters.

4. Discussion

This meta-analysis of 14 voxel-based morphometry studies included 743 UHR individuals matched with 588 HC. The aim is to investigate the potential structural markers underlying the transition risk to psychosis and differentiate UHR individuals from healthy subjects. We also conducted a systematic review of cortical thickness studies, including 700 UHR subjects matched with 469 healthy controls, to comprehensively explore the underlying structural pathology. Gray matter volume and cortical thickness showed conjoint and dissociated alterations in the thalamo-cortical networks. To the best of our knowledge, this neuroimaging meta-analysis is the first to focus on UHR subjects using SDM on

Table 1
VBM and cortical thickness studies included in the review.

Study	Research center	Assessment instrument	Medication (baseline)	Specification		MRI scanner	Software	Smoothing (FWHM)
Cannon et al. (2015)	USA	SIPS	Yes	Cortical thickness	Longitudinal	3 T	FSf5.2	NA
Nakamura et al. (2013)	Japan	CAARMS	Yes	VBM-GM volume	Cross-sectional	1.5 T	SPM8	10 mm
Klauser et al. (2015)	Singapore	CAARMS	No	VBM-GM volume Cortical thickness	Cross-sectional	3 T	SPM8 FSf5.1	8 mm 25 mm
Smieskova et al. (2012)	Switzerland	CAARMS	No	VBM-GM volume	Longitudinal	3 T	SPM8	8 mm
Dukart et al. (2017)	Switzerland	CAARMS	No	VBM-GM volume VBCT	Cross-sectional	3 T	SPM12	8 mm
Lincoln and Hooker (2014)[a]	USA	SIPS	No	VBM-GM volume	Cross-sectional	3 T	SPM8	8 mm
Benetti et al. (2013)	UK	CAARMS	Yes	VBM-GM volume VBCT	Cross-sectional	3 T	SPM8	6 mm
Zhao et al. (2018)>	China	SIPS	No	VBM-GM volume	Cross-sectional	3 T	SPM8	6 mm
Ziermans et al. (2012)	The Netherlands	SIPS+BSABS	Yes	Cortical thickness	Longitudinal	1.5 T	CLASP	20 mm
Tognin et al. (2014)	UK, Switzerland, Germany, Australia	CAARMS+BSIP +BSABS	Yes	VBCT	Longitudinal	1.5 T	SPM8	6 mm
Witthaus et al. (2009)	Germany	SIPS	Yes	VBM-GM volume	Cross-sectional	1.5 T	SPM2	12 mm
Whitford et al. (2012)[b]	Australia	CAARMS	No	VBM-GM volume	Cross-sectional	3 T	SPM2	12 mm
Nenadic et al. (2015)	Germany	CAARMS	No	VBM-GM volume	Cross-sectional	3 T	SPM8	12 mm
Mechelli et al. (2011)	UK, Switzerland, Germany, Australia	CAARMS	No	VBM-GM volume	Cross-sectional	1.5 T, 3 T	SPM8	8 mm
Iwashiro et al. (2016)	Japan	SIPS	Yes	VBM-GM volume	Cross-sectional	3 T	SPM8	8 mm
Lee et al. (2013)	South Korea	SIPS	No	VBM-GM volume	Cross-sectional	3 T	FSL5.0	3 mm
Heinze et al. (2015)	Australia	CAARMS	No	VBM-GM volume	Longitudinal	1.5 T	SPM8	8 mm
Jung et al. (2011)	South Korea	CAARMS	Yes	Cortical thickness	Cross-sectional	1.5 T	CLASP	20 mm
Haller et al. (2009)	Switzerland	BSIP	Yes	Cortical thickness	Cross-sectional	1.5 T	BV1.7	NA
Bakker et al. (2016)	The Netherlands	SIPS	No	Cortical thickness	Cross-sectional	3 T	FSf	10 mm

Abbreviations: BSABS, the Bonn Scale for the Assessment of Basic Symptoms; BSIP, the Basel Screening Instrument for Psychosis; BV, BrainVoyager; CAARMS, the Comprehensive Assessment for at Risk Mental State; FSf, FreeSurfer; GM, gray matter; NA, not available; SIPS, the structured interview for prodromal syndromes; VBCT, voxel-based cortical thickness; VBM, voxel-based morphometry.
[a] In this study, participants' symptoms did not have to meet duration and frequency criteria for the prodromal syndrome.
[b] Twenty-five out of 58 ultra-high risk individuals with a history of Herpes Simplex Virus type 1 exposure.

the whole brain basis. Several meta-analyses have studied the neuroimaging predictors of the transition to psychosis. However, not only clinical high-risk subjects were included but also genetic high-risk subjects, which increased the heterogeneity and confounded the results. In addition, ROI studies were included, which increased the potential bias induced by the selection of interest regions (Pearlson and Calhoun, 2007; Wang et al., 2017).

Consistent with studies in patients with first-episode schizophrenia (Andreasen et al., 2011; Gutierrez-Galve et al., 2015), decreased gray matter volume in widespread frontal regions was the most prominent finding in our meta-analysis. These regions are a part of the executive network and play an indispensable role in working memory and attention (Seeley et al., 2007), which have been impaired in both UHR subjects and patients with schizophrenia. Furthermore, cortical thickness studies presented a specific cortical atrophy in the superior and medial frontal gyrus. The atrophy may have partly decreased gray matter volume in this region. Similarly, few fMRI studies on patients with clinical high-risk for psychosis showed reduced activation in the inferior, medial, and superior frontal gyrus than healthy controls, regardless of the fMRI task used. This finding was also proven by an fMRI meta-analysis using SDM. Considering the neural diathesis-stress model, Valli et al. (2016) found that the UHR group had a marked positive correlation between cortisol awakening response and gray matter volume, with impaired responsivity of the HPA axis linked to the smaller gray matter in the prefrontal and parahippocampal/fusiform gyrus. These conjoint structural and functional abnormalities in extending frontal regions indicate that alterations are indeed present before the onset of psychosis and are thus early markers of psychosis in the UHR population. This finding provides support that the prefrontal gyrus plays an important role in the neurobiology of schizophrenia.

Significantly increased superior temporal gyrus (STG) and fusiform gyrus were also found in our results, although the inter-study heterogeneity cannot be neglected. The primary auditory and neocortical language regions, superior temporal gyrus, and insula are the core regions responsible for the positive symptoms, such as delusions, hallucinations, and disorganized speech (Augustine, 1996; Kim et al., 2000; Kurachi et al., 2018). However, the directionality of gray matter volume abnormalities in these regions has provoked intense debates in several

Table 2
Demographic characteristics of subjects and coordinates of VBM and cortical thickness studies in the review.

Study	UHR			HC			*P*-value	Coordinates
	No.	M/F	Age	No.	M/F	Age		
VBM								
Nakamura et al. (2013)	14	10/4	18.9	51	30/21	23.9	$P < 0.05$(FWE)	0
Klauser et al. (2015)	69	47/22	21.5	32	17/15	23.0	$P < 0.001$(FDR)	2
Smieskova et al. (2012)	31	22/9	24.8	19	10/9	26.6	$P < 0.05$(FWE)	0
Dukart et al. (2017)	59	43/16	24.7	26	12/14	27.7	$P < 0.05$(FWE)	2
Lincoln and Hooker (2014)	22	NA	22.0	21	NA	22.2	$P < 0.05$(FWE)	10
Benetti et al. (2013)	21	9/12	22.1	23	12/11	24.2	$P < 0.05$(FWE)	3
Zhao et al. (2018)	26	18/8	21.0	39	19/20	22.2	$P < 0.001$-uncorrected (MCC)	0
Witthaus et al. (2009)	30	20/10	25.1	29	17/12	25.7	$P < 0.05$-uncorrected (FWE)	9
Whitford et al. (2012)	58	32/26	19.4	19	7/12	21.0	$P < 0.05$ (FWE)	0
Nenadic et al. (2015)	43	21/22	23.7	49	26/23	23.8	$P < 0.001$-uncorrected	6
Mechelli et al. (2011)	182	66/116	23.0	167	104/63	23.5	$P < 0.05$ (FWE)	5
Iwashiro et al. (2016)	23	13/10	21.3	16	10/6	23.8	$P < 0.05$ (FDR)	0
Lee et al. (2013)	32	22/10	20.6	32	20/12	21.9	$P < 0.05$(FWE)	1
Heinze et al. (2015)	133	77/56	20.2	65	40/25	22.1	$P < 0.01$(FWE)	6

Study	UHR			HC			*P*-value	Regions
	No.	M/F	Age	No.	M/F	Age		
Cortical thickness								
Cannon et al. (2015)	274	171/103	19.2	135	73/62	20.5	$P \leq 0.01$ (FDR)	UHR-C vs HC & UHR-NT (rates of change) ↓: R SFG, MFG, medial orbital frontal gyrus
Klauser et al. (2015)	69	47/22	21.5	32	17/15	23.0	$P < 0.001$ (FDR)	UHR vs HC ↑: R frontal pole
Dukart et al. (2017)	59	43/16	24.7	26	12/14	27.7	$P < 0.05$ (FWE)	UHR vs HC ↑: Bi SPL, L IOG, AG, MOG, occipital pole, cerebellum exterior ↓: Bi SFG, Bi MFG, precentral gyrus
Benetti et al. (2013)	21	9/12	22.1	23	12/11	24.2	$P < 0.05$ (FWE)	UHR vs HC ↓: R STG
Ziermans et al. (2012)	43	29/14	15.6	30	15/15	15.9	$P < 0.05$ (FDR)	UHR-C vs HC ↓: L AG, precuneus, temporo-parieto-occipital area
Tognin et al. (2014)	167	105/62	23.1	150	99/51	23.4	$P < 0.05$ (FWE)	0
Jung et al. (2011)	29	15/14	22.24	29	15/14	23.24	$P < 0.01$ (FDR)	UHR vs HC ↓: L STG, R lingual cortex, R IFC, R IPC, R MTC, Bi ACC, parahippocampal, MFG
Haller et al. (2009)	20	12/8	24.9	20	12/8	23.5	$P < 0.05$	0
Bakker et al. (2016)	18	8/10	22.7	24	14/10	23.4	$P < 0.05$ (FDR)	0

Abbreviations: ACC, anterior cingulate cortex; AG, angular gyrus; Bi, bilateral; FDR, false discovery rate; FEW, family-wise error correction; HC, healthy control; IFC, inferior frontal cortex; IOG, inferior occipital gyrus; IPC, inferior parietal cortex; L, left; MCC, multiple comparison correction; M/F, male/female; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTC, middle temporal cortex; No., number; R, right; SFG, superior frontal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; UHR, ultra-high risk; UHR-C, ultra-high risk subjects who converted to psychosis; UHR-NC, ultra-high risk subjects who did not convert to psychosis; VBM, voxel-based morphometry.

studies (Borgwardt et al., 2007; Haijma et al., 2013; Honea et al., 2005; Klauser et al., 2015). Few longitudinal studies that focused on first-episode patients with schizophrenia, the progressive gray matter reduction of the STG was found, which is linked to low improvement in positive psychotic symptoms (Li et al., 2018; Takahashi et al., 2010). Moreover, increased gray matter volume was found in the temporal

Table 3
Regions of significant differences in gray matter volume and cortical thickness between UHR individuals and healthy controls.

Region	Maximum				Cluster breakdowns	Jackknife
	MNI coordinates x, y, z	SDM z-score	*P* value	Voxels		
Increased GM volume						
Median cingulate	6, −14, 30	1.034	0.001181841	234	Corpus callosum. R median cingulate/paracingulate gyri, BA 23.L median cingulate/paracingulate gyri, BA 23.	12/14 (Nenadic et al.; Klauser et al.)
R fusiform gyrus, BA 20	22, 0, −50	1.051	0.000541866	202	R fusiform gyrus, BA 36, BA 20.	13/14 (Nenadic et al.)
L temporal pole, superior temporal gyrus, BA 28	−18, 6, −34	1.048	0.000557363	164	L parahippocampal gyrus, BA 28. L temporal pole, middle temporal gyrus, BA 36. L temporal pole, superior temporal gyrus.	13/14 (Nenadic et al.)
R thalamus	8, −18, 20	1.039	0.000872195	60	R thalamus.	13/14 (Nenadic et al.)
Decreased GM volume						
R gyrus rectus, BA 11	4, 38, −18	−2.109	0.000392199	480	R gyrus rectus, BA 11. L gyrus rectus. R superior frontal gyrus, medial orbital. L superior frontal gyrus, medial orbital.	13/14 (Mechelli et al.)
R superior frontal gyrus, medial, BA 10	10, 56, 14	−2.321	0.000061929	287	Corpus callosum. R superior frontal gyrus, medial & dorsolateral, BA 10. R anterior cingulate/paracingulate gyri, BA 32.	12/14 (Mechelli et al.; Heinze et al.)
L superior frontal gyrus, orbital part, BA 11	−20, 52, −14	−2.228	0.000108361	136	L middle frontal gyrus, orbital part, BA 11. L superior frontal gyrus. Left striatum.	14/14

Abbreviation: BA, Brodmann area; GM, gray matter; L, left; R, right; MNI, Montreal Neurological Institute Space; SDM, seed-based d mapping.

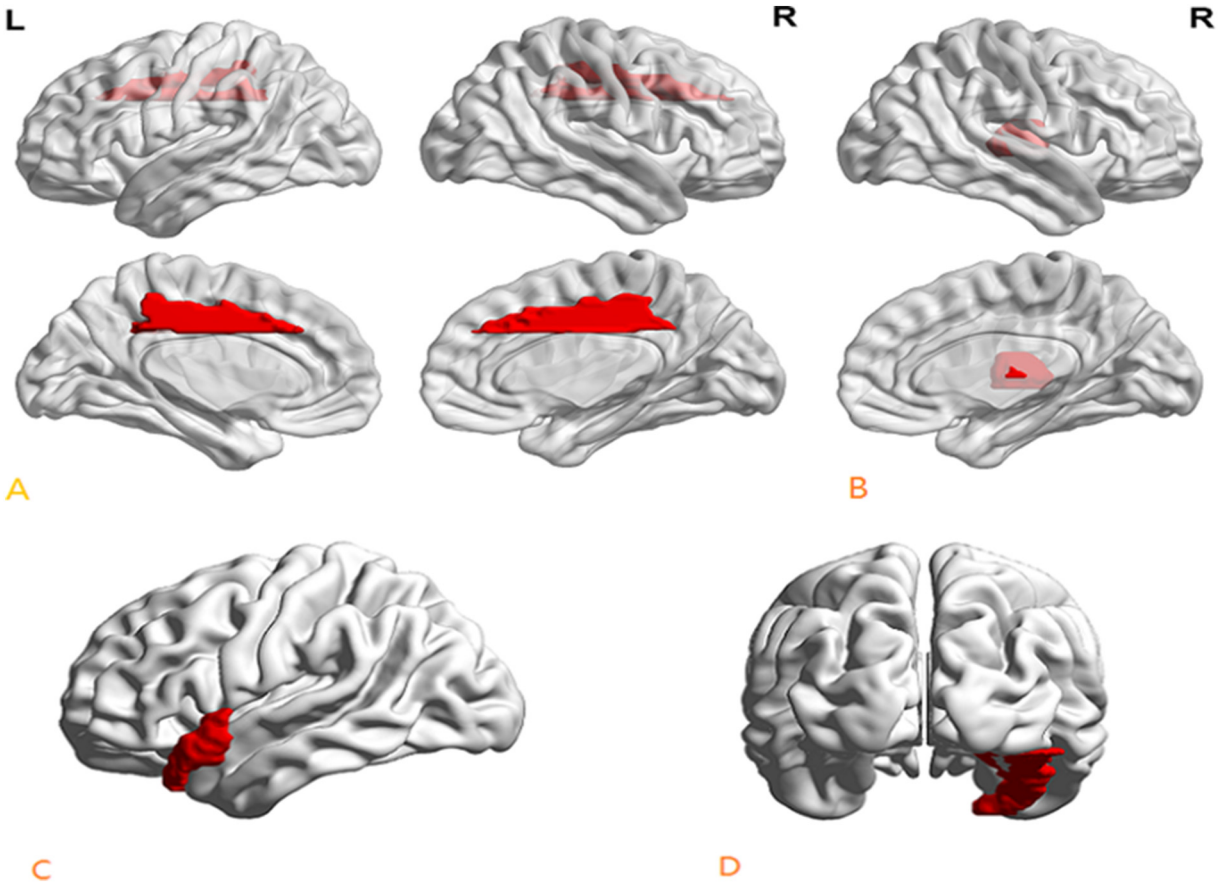


Fig. 2. Areas of increased gray matter volume in individuals at ultra-high risk for psychosis compared with healthy controls in the meta-analysis of voxel-based morphometry studies. (A) Median cingulate; (B) right thalamus; (C) left superior temporal gyrus; (D) right fusiform gyrus.

regions of patients with schizophrenia and psychosis (Borgwardt et al., 2007; Cooper et al., 2014; Dukart et al., 2017; Heinze et al., 2015; Koutsouleris et al., 2015; Ren et al., 2013). Notably, these findings were in line with our results. The first possible explanation is that VBM and cortical thickness revealed different pathophysiological processes in the early phase. In other words, increased gray matter is more likely due to the changes in the surface area or cortical folding rather than changes in cortical thickness (Benetti et al., 2013; Hutton et al., 2008). Second, the pattern of gray matter volume varies with age group. Older subjects with UHR would likely result in a more prominent structural decrease than the HC (Dukart et al., 2017). Third, other demographic differences, genetic predisposal, and different MRI scanners or parameters employed in the method section require consideration. For example, 3 T scanners with novel preprocessing pipelines enhance structural segmentation, thereby increasing detection sensitivity relative to that of a 1.5 T scanner (Dukart et al., 2017). Similarly, VBM8 provides a more optimized segmentation and normalization than VBM2 (Lui et al., 2009; Ren et al., 2013). Fourth, it may be a kind of region- and state-specific compensation behavior response to an ongoing pathological process. Notably, severe gray matter reduction in the STG and fusiform gyrus during the early phases of schizophrenia can be ameliorated with antipsychotics, and thus the early recognition of subjects with UHR and early intervention may prevent or retard full-blown psychosis.

The thalamus, which is composed of several nuclei with different cytoarchitecture and functions (Cho et al., 2018), is a complex structure associated with emotional experience and expression (Wang et al., 2017) and cognitive functions, such as memory, attention, and

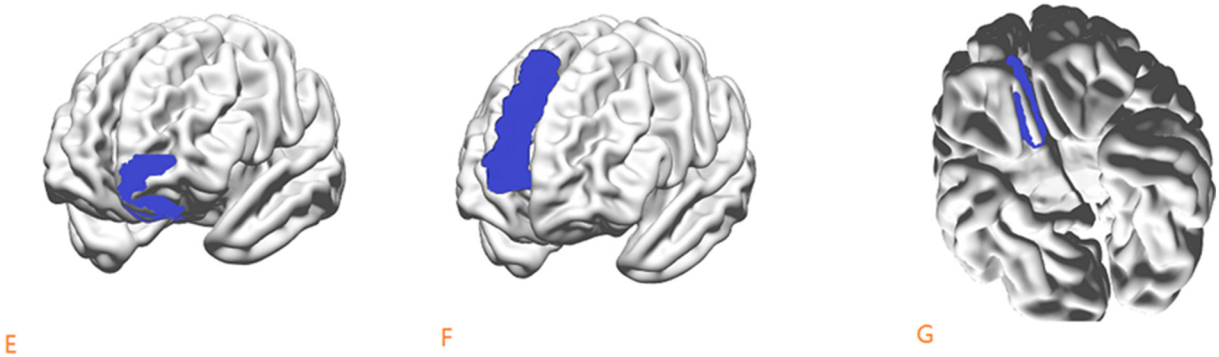
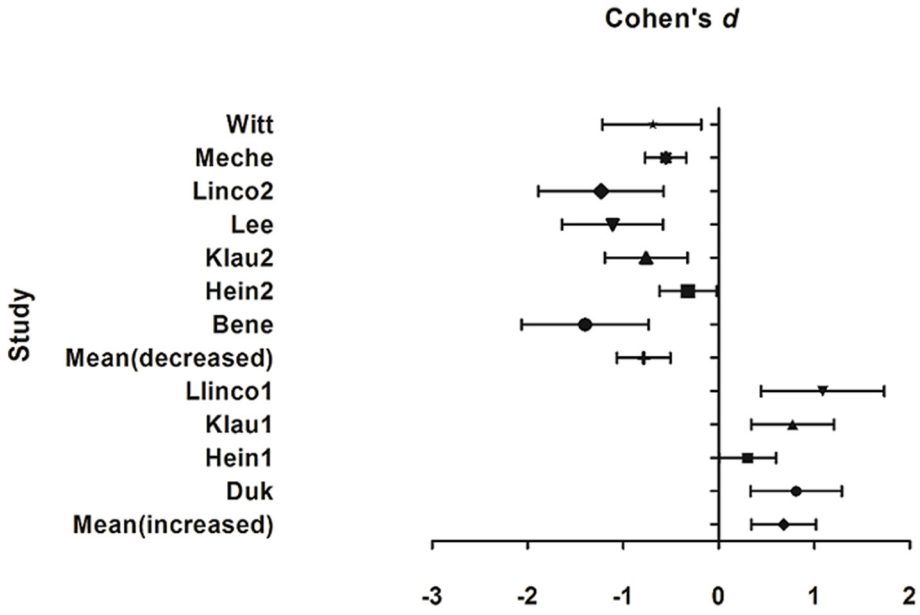


Fig. 3. Areas of decreased gray matter volume in individuals at ultra-high risk for psychosis compared with healthy controls in the meta-analysis of voxel-based morphometry studies. (E) Left superior frontal gyrus, orbital part; (F) right superior frontal gyrus, medial part; (G) right gyrus rectus.



Sample	*d*	SE	lowerCI	upperCI	*P*
Duk	0.81	0.244	0.332	1.288	0.000896215
Hein1	0.301	0.152	0.003	0.599	0.048018456
Klau1	0.773	0.221	0.34	1.206	0.000470638
Linco1	1.087	0.329	0.443	1.732	0.00094676
Mean(increased)	0.679	0.174	0.338	1.019	0.000093222

Sample	*d*	SE	lowerCI	upperCI	*P*
Bene	−1.398	0.34	−2.064	−0.732	0.000038588
Hein2	−0.323	0.152	−0.621	−0.024	0.034066904
Klau2	−0.76	0.221	−1.192	−0.024	0.034066904
Lee	−1.111	0.27	−1.64	−0.583	0.00003784
Linco2	−1.233	0.335	−1.89	−0.576	0.000235209
Meche	−0.555	0.109	−0.769	−0.341	0.000000369
Witt	−0.69	0.269	−1.217	−0.164	0.010150183
Mean(decreased)	−0.786	0.143	−1.067	−0.505	0.000000041

Fig. 4. Forest plot showed effect size (Cohen's d) of peak height meta-analysis for the corrected threshold studies. Abbreviation: Bene, Benetti et al. (2013); Duk, Dukart et al. (2017); Hein, Heinze et al. (2015); Klau, Klauser et al. (2015); Lee, Lee et al. (2013); Linco, Lincoln and Hooker (2014); Meche, Mechelli et al. (2011); Witt, Witthaus et al. (2009).

sensory-guided actions (Mitchell et al., 2008; Wilke et al., 2010). Impaired thalamus was found in schizophrenic patients as manifested by a reduced number of neurons (Bogerts, 1993), altered brain activation (Heckers et al., 2000), and decreased volume (Adriano et al., 2010; Haijma et al., 2013). By contrast, we found an increased right thalamus volume without significant inter-study heterogeneity and publication bias in our meta-analysis, providing another support to the work of Ren et al. (Ren et al., 2013). Apart from an early-course compensation or neuroinflammatory response in the early state of the illness, several factors possibly merit the discrepancy. First, those findings were shown in first-episode and chronic patients with schizophrenia. Hence, illness duration, medications, and demographic characteristics, such as age, which is associated with the neuronal overgrowth problem and pruning deficiency, are inevitable confounding factors. Especially, patients with prominent negative symptoms are likely to show increased gray matter volume (Ren et al., 2013). Furthermore, available approaches for investigating this region are limited, whether postmortem or in vivo. Some cytoarchitectural changes, such as dendritic spines, cannot be observed through imaging methods (Cho et al., 2018). Our meta-analysis considered a large number of samples for a sufficient statistical means to identify hypertrophic changes, which were undetectable in previous studies. Future studies conducting frequent neuroimaging assessments may be helpful to unfold the actual development trajectories of the thalamus during imminent psychosis.

The importance of prefrontal volumetric abnormalities in schizophrenia and UHR individuals was also confirmed in the subgroup of UHR subjects who converted to full-threshold psychosis (UHR-C) through a decreased dorsolateral prefrontal cortex (dlPFC) than those who did not (UHR-NC). The dlPFC is an important part of the executive control network, which is impaired in schizophrenia and UHR subjects and may play a pivotal role in psychotic disorder (Heinze et al., 2015). Apart from these involved longitudinal VBM studies, Koutsouleris et al. (2010) and Dazzan et al. (2012) found a reduced gray matter volume in the wide frontal areas. Notably, UHR-C individuals had more gray matter loss in the right superior frontal, orbital gyrus, and left rectal gyrus with a steeper rate than UHR-NT individuals (Borgwardt et al., 2008; Dietsche et al., 2017). Although uncorrected *P* value was adopted, thinning cortical thickness was detected in the left inferior frontal gyri (Tognin et al., 2014). The thinning is related to the decreased gray matter volume and may have partly contributed to the reduction of the volume in this area. Similar to the finding on UHR individuals and HC, the changes in the gray matter volume in the wide temporal gyrus may have been caused by the disturbances in the auditory network in subjects with UHR-C and with more severe and persistent auditory hallucinations than subjects with HC and even UHR-NC. The anterior cingulate cortex (ACC) is a central station that assigns control and processes stimuli and the salience of emotion associated with the widespread cortex, including the prefrontal and parietal cortices, as well as the motor

system, amygdala, hypothalamus, hippocampus, and anterior insula (Allman et al., 2001; Bush et al., 2000). Patients with schizophrenia have impaired ACCs, experience difficulty in problem solving, and show abnormal error-detection function (Holroyd et al., 2004; Posner and DiGirolamo, 1998). The significant gray matter alteration in the ACC of UHR-C individuals than UHR-NC individuals may be responsible for the appearance of subthreshold symptoms and may play a role in distinguishing these two subgroups.

Interestingly, unlike progressive anatomical changes in the frontal and temporal regions in individuals with UHR-C, disturbance in the thalamus in individuals with UHR may indicate UHR symptomatology, which can be regarded as a potential marker specific to the UHR stage instead of the onset of psychosis or, alternatively, the abnormal thalamus may represent a potential resilient factor leading to a less possibility to conversion according to those involved longitudinal studies and considering the relatively limited number of UHR-C individuals in all recruited subjects. Surprisingly, few longitudinal studies failed to determine significant differences between UHR-C and HC or UHR-NC. Several possible explanations exist. First, the UHR samples of each study are heterogeneous. That is, they present different clinical and cognitive characteristics. These differences may indicate distinct underlying pathophysiological changes. Moreover, the reasons that individuals with psychosis show high levels of functioning or those who are considered nonconverters suffer deteriorated functioning are unknown. Therefore, the converted but high-functioning individuals may not show anatomical alterations that are consistent with the changes reported in individuals with UHR-C and schizophrenia. Second, the effects of age on the findings cannot be discounted. For example, Gogtay et al. (2011) reported that neuroanatomical disparities are present in patients with early-onset (before 18 years) schizophrenia and those with adult-onset schizophrenia.

This study has several limitations. The first limitation of the meta-analysis is the presence of subgroups in the UHR subjects with different levels of psychosis risk as well as recruitment strategies: a few of them will develop psychosis, whereas others will not. Considering that not all UHR subjects will transit to psychosis and the benefits and time point of medication intervention remain under discussion, conducting further longitudinal studies is important to clarify the observed findings, which exactly pertain to the subsequent onset of psychosis. Second, although we attempt to diminish the effect of variables and those with history of antipsychotic use received extremely low doses of drugs over short periods, other confounding factors, such as affective comorbidities (e.g., depression and anxiety), substance abuse, and ethnic differences, could increase heterogeneity. Third, we only use peak voxels in SDM meta-analysis that may omit certain changes, which are subtle in individual studies but may be statistically significant in large-scale studies (Wang et al., 2017). Finally, cortical thickness changes in UHR subjects have only been investigated by a few studies. Hence, we did not conduct a meta-analysis of cortical thickness alterations, consequently requiring a careful interpretation of the results.

Despite these limitations, our meta-analysis overcame the problem of small sample size and recruitment of several valuable longitudinal studies. Thus, UHR subjects are shown to display a conjoint and dissociated, consistent, and state-specific gray matter volume and cortical thickness alterations in widespread brain regions, especially within the thalamocortical networks. This finding emphasizes the core roles of these regions in the pathophysiology of early psychosis. Compared with cortical thickness abnormalities, which are likely to emerge as psychosis occurs, gray matter volume changes may appear before the onset of psychosis. Such bidirectional abnormalities indicate a complex portrait of misbalanced cortical development in the UHR group and a dynamic process amid the phase between at-risk state and overt psychosis. Thus, they may be reliable predictive markers suggesting an increased vulnerability to psychosis. We hope that these findings, along with other non-neuroimaging data (e.g., functional and cognitive level), will fill the gap between neuroscience and clinical practice to facilitate early intervention and improve the outcomes of the illness.

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Contributors

Drs. Guo W., Chen J. and Zhao J. designed the study. Ding Y., Ou Y. and Pan P. searched for studies. Ding Y., Shan X. and Liu F. analyzed these included data. Ding Y. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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