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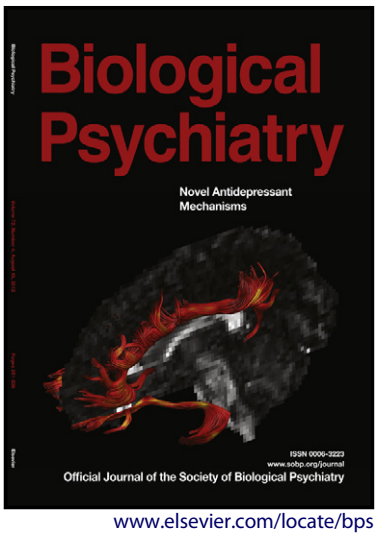

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Discrete Alterations of Brain Network Structural Covariance in Individuals at Ultra-High Risk for Psychosis

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Abstract

Background. Investigation of aberrant large-scale brain networks offers novel insight into the role these networks play in diverse psychiatric disorders, such as schizophrenia. While there are studies reporting altered functional brain connectivity in participants at ultra-high risk (UHR) for psychosis, it is unclear whether these alterations extend to structural brain networks.

Methods. Whole-brain structural covariance patterns of 133 participants at UHR for psychosis (51 of whom subsequently developed psychosis) and 65 healthy controls (HC) were studied. Following data pre-processing (using VBM8), the mean signal in seed regions relating to specific networks (visual, auditory, motor, speech, semantic, executive, salience and default-mode) were extracted and voxel-wise analyses of covariance were conducted to compare the association between whole brain signal and each seed region for UHR and HC individuals. UHR participants who transitioned were compared to those who did not.

Results. Significantly reduced structural covariance was observed in the UHR sample compared to HC for the default-mode network, and increased covariance for the motor and executive control networks. When those who transitioned to psychosis were compared with those who did not, aberrant structural covariance was observed in the salience, executive-control, auditory and motor networks.

Conclusions. Whole-brain structural covariance analyses revealed subtle changes of connectivity of the default-mode, executive control, salience, motor and auditory networks in UHR individuals for psychosis. Although we found significant differences, these are small changes, and tend to reflect largely intact structural networks.

Schizophrenia is associated with substantial brain changes, most prominently in frontal and temporal areas [1]. The period preceding the onset of schizophrenia and other psychotic disorders is characterised by non-specific symptoms such as anxiety and depressed mood, attenuated psychotic symptoms (e.g. delusions or hallucinations) and a decline in social and role functioning. To detect young people in the prodromal phase of psychotic illness, these characteristics have been operationalized and are known as the at-risk mental state (or ultra-high or clinical high risk for psychosis) [2]. According to a recent meta-analysis, rates of transition to frank psychosis in individuals presenting with these features are estimated to be approximately 22% over twelve months, increasing to 29% after two years and 36% after three years [3]. Neurobiological abnormalities in such individuals appear to be qualitatively similar but less severe than in schizophrenia [4]. This relative sparing in individuals at ultra-high risk (UHR) for psychosis highlights the importance of early intervention [5] to reduce the risk of pronounced and possibly non-reversible structural brain alterations associated with progression to a first episode of psychosis [6].

Previous work has concentrated on neurobiological correlates and predictors of psychotic illness with a region-of-interest (ROI) perspective [7, 8] or voxel-based morphometry (VBM) [9] – that is, investigation has focused on how gray matter volume alterations may be associated with schizophrenia or predict its onset in high risk samples. Such ROI studies have identified smaller frontal [10], insular [11], parahippocampal [10, 12] and superior temporal gyri [13] volumes, characterising the UHR individuals and/or predating the onset of psychosis, which has generally been replicated by VBM studies [9]. Such changes, which are also associated with schizophrenia, are assumed to be distributed, involving inter-connected brain networks rather than focal regions [14]. An alternative approach is therefore to presume that it is dysfunction at the *network* level that is associated with the disorder. Large-scale brain networks offer a striking paradigm to look at the cognitive and affective dysfunction in psychiatric disorders. Network abnormalities may develop before the onset of frank psychotic illness: it has, for example, been found that UHR individuals with higher levels of symptoms demonstrate a significantly decreased contribution of the anterior cingulate cortex (ACC) to task-relevant network organisation compared to less symptomatic participants and healthy controls (HC) [15].

The large-scale networks of most interest in schizophrenia are the so-called “salience” (SN), “default-mode” (DMN) and “executive control” networks (ECN). The SN is anchored in the dorsal anterior cingulate and fronto-insular cortices; the DMN consists of the posterior cingulate (PCC) and medial prefrontal cortices (mPFC),

medial temporal lobe, and angular gyrus; and the ECN is a fronto-parietal system anchored in the parietal and dorsolateral prefrontal cortices (dlPFC) [16].

The SN detects the most salient internal and environmental stimuli and switches between other large-scale networks, such as the DMN and ECN, in order to guide behavior, e.g. to enable access to attention and working memory resources when needed [17]. The observation of insular activation during hallucinations suggests that the SN is creating heightened salience during otherwise normal activity, which supports the notion of an insular dysfunction model of psychosis [18]. Furthermore, we have shown that there are progressively declining insular volumes in UHR patients who subsequently transitioned to psychosis, when compared to those who did not transition and HC [11]. This misattribution of salience to internally generated mental events, such as hallucinations, would in turn be expected to promote activation of the DMN [17] and lead to an impaired suppression of DMN activity during task performance [19, 20]. Individuals with a familial risk for psychosis have been assessed in functional magnetic resonance imaging (fMRI) studies and found to show altered resting-state connectivity within the DMN between the PCC, precuneus and prefrontal areas [21-23]. This finding was further supported by a failure to properly modulate the ventromedial prefrontal cortex (vmPFC) and precuneus during self-referential processes in individuals with a family history as compared to controls [21]. This notion is consistent with the model of basic self-disturbance in schizophrenia and may be associated with observed source monitoring deficits [24, 25]. Resting-state fMRI studies have further shown that the typically observed anti-correlated relationship between the SN and DMN, specifically between the medial

prefrontal and dlPFC, and the right insula and PCC, was absent in UHR subjects [26], and that UHR subjects show reduced resting-state connectivity between diverse frontal and subcortical regions [27].

Another way to investigate brain connectivity is by means of structural covariance analyses, a method that considers the correlation of gray matter volume between different areas of the brain. These analyses have shown that gray matter volume of one brain area is a good predictor of the volume of the respective contralateral area [28]. A substantial, but not complete, overlap between structural covariance and the blood oxygen level-dependent signal fluctuations (as measured by fMRI) and white matter connections (measured by diffusion tensor imaging, DTI) has been detected [29]. As differences in the structure of one brain region often co-vary with differences in other brain areas [29], studying structural covariance gives additional insight into brain structure and composition. Considering a mental disorder such as schizophrenia, which is hypothesized to involve dis-connectivity of frontal brain structures [30], structural covariance analyses (SCAs) are informative on the whole-brain level in terms of inter-connections between diverse brain areas. SCAs in individuals with schizophrenia with severe auditory hallucinations showed positive correlations between gray matter volume and hallucination severity in the left inferior frontal gyrus (IFG) and patterns of structural covariance between the left IFG and left middle temporal gyrus, right IFG, right hippocampus and insula bilaterally [31]. A recent study discovered different patterns of structural covariance in first-episode, drug-naïve schizophrenia patients as compared to HC, involving the amygdala, insula and postcentral gyrus [14].

The aim of this study was to investigate whole-brain structural covariance patterns of eight large-scale networks in young people identified as UHR for psychosis. Our approach was based on that of Zielinski and colleagues [32], specifically investigating the DMN, SN, and ECN, which were shown to play a pivotal role in the development of psychotic disorders. Furthermore, disturbances of the visual and auditory network might potentially be associated with visual and auditory hallucinations, and the speech network be implicated in disorganised speech [33], which is supported by reduced brain activation of frontal areas and the insula during a word generation task in schizophrenia patients [34]. Poor motors skills and a delayed motor development were observed in high-risk individuals [35]. These observations might lead to the presumption of altered structural covariance in the semantic and motor network. Considering the novelty of this approach, dissimilarities with the nature of other imaging modalities described so far, and often inconsistent findings, no strong directional hypotheses can be inferred. However, taking into account the important role of the insula in psychotic disorders and high-risk individuals, increased covariance of the salience network, and in turn altered covariance of the DMN and ECN, in UHR as compared to HC, and those UHR individuals who transition to psychosis as compared to those who do not, is hypothesized. Exploratory analyses for the other five networks are conducted as well.

Methods and Materials

Participants

UHR for psychosis participants (*n*=133) were recruited through the Personal Assessment and Crisis Evaluation (PACE) Clinic, Orygen Youth Health, Melbourne, Australia [36]. UHR criteria were defined using the Comprehensive Assessment of At-Risk Mental States (CAARMS) [37]. These are 1) Attenuated Psychotic Symptoms, 2) Brief Limited Intermittent Psychotic Symptoms, and/or 3) trait vulnerability.

For the Attenuated Psychotic Symptoms criterion ("APS") (1), symptoms must be present for at least once a week, with a frequency of at least several times per week *(n=94)*. The Brief Limited Intermittent Psychotic Symptoms (''BLIPS''; 2) criterion refers to psychotic symptoms at the severity and frequency of frank psychosis but which spontaneously resolve within 7 days *(n=30)*. Trait vulnerability (3) refers to young people with a first degree relative with psychotic illness, or schizotypal personality disorder in the individual, accompanied by a substantial deterioration in functioning, maintained for at least a month within the past year, or by chronic low functioning *(n=49)* [37]. 58 individuals displayed APS, 15 BLIPS, 23 trait vulnerability, 11 APS and BLIPS, 22 APS and trait vulnerability, 1 BLIPS and trait vulnerability, and 3 individuals belonged to all three groups.

HC individuals (n=65) were recruited from similar socio-demographic regions to UHR participants via auxiliary hospital staff and advertisements. They had no personal

history of mental illness or a first-degree relative with a history of psychotic disorder (assessed using the SCID-I screen for DSM-IV [33] and personal report). All participants were aged between 13 and 30 at the time of scan, and had experienced no previous psychotic episodes or treatment with neuroleptics.

Exclusion criteria for both groups were IQ<70 and a history of neurological disorder, seizures, or significant head injury, thyroid dysfunction, or corticosteroid use, and any contraindications for MRI. Participants had normal or corrected-to-normal vision and hearing and spoke English as their preferred language. All participants gave written informed consent and this study was approved by the local research and ethics committee.

Outcomes

UHR individuals were followed up in the medium to long-term by means of operationalized criteria for psychosis onset [38] over a 6 to 13 year period ($Median_{time}$ to follow-up: 10.6, range: 6.5-12.8 years) [39]. Transition to psychosis was defined as at least one fully positive symptom several times a week for more than one week. Transition was assessed using a combination of the Comprehensive Assessment of Symptoms and History (CASH; [40]) and the Brief Psychiatric Rating Scale (BPRS; [41]) for 15 participants in 1995 who were seen at PACE before the CAARMS was developed. From 1996 to 2001, psychosis status was determined using the CAARMS (n=118) [38, 39]. Over the follow-up period, 51 UHR participants (38.4%) transitioned to psychosis (UHR-P) whereas 82 did not (UHR-NP). The BPRS as well as other scales such as the Scale for the Assessment of Negative Symptoms (SANS) [42]

were administered to all participants at their baseline assessment at identification as UHR.

Data acquisition and pre-processing

Structural scans were acquired at baseline using a 1.5T MRI scanner (GE Signa; General Electric Medical Systems, Milwaukee, Wisconsin). A 3-dimensional volumetric spoiled gradient–recalled echo in the steady state sequence generated 124 contiguous 1.5-mm coronal sections. Imaging parameters were as follows: echo time, 3.3 milliseconds; repetition time, 14.3 milliseconds; flip angle, 30°; matrix size, 256x256; field of view, 24x24-cm matrix; and voxel dimensions, 0.9375x0.9375x1.5 mm. Head movement was minimized by using foam padding and Velcro straps across the forehead and chin. The images were calibrated fortnightly with the same proprietary phantom to ensure the stability and accuracy of measurements.

T1-weighted images were manually reoriented and centered on the anterior commissure and normalised into standard space and segmented into gray matter, white matter and cerebro-spinal fluid using a VBM8-toolbox (http://dbm.neuro.uni-jena.de/spm) in SPM8 (SPM8, Friston, The Welcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). The VBM8 toolbox used a unified segmentation approach that integrates tissue classification, image registration and inhomogenous bias correction [43]. The resulting segments were then smoothed using a 8-mm full-width at half-maximum Gaussian kernel, to improve spatial resolution of the analyses. To study network structural covariance, gray matter intensities were derived using 4-mm-radius spherical seed ROI chosen in accordance with Zielinski at al. [32] and defined with a MarsBar toolbox

(http://marsbar.sourceforge.net) in SPM8 [44]. Seed regions were bilaterally defined in the visual (primary visual cortex, calcarine sulcus, (-) 9 -81 7), auditory (primary auditory cortex, Heschl's gyrus, (-) 46 -18 10), sensorimotor (primary motor cortex, precentral gyrus, (-) 28 -16 66), speech (inferior frontal gyrus, pars opercularis, (-) 50 18 7), semantic (temporal pole, (-) 38 10 -28), salience (frontoinsular cortex, (-) 38 26 -10), executive control (dorsolateral prefrontal cortex, (-) 44 36 20), and default-mode (angular gyrus, (-) 46 -59 23) networks [45-48] (see Table S1). In order to establish whether the choice of seed selection mattered, we additionally included respectively two further seeds from the three networks that we were particularly interested in (SN, pre- and supragenual ACC (0 40 16/ (-) 4 28 24); ECN, inferior parietal lobule ((-) 38 -53 45/ (-) 54 -50 50); DMN, PCC ((-) 2 -50 36) and mPFC ((-) 2 58 -8).

Initially, we determined whole-brain patterns of seed-based structural covariance in both hemispheres in each group separately and used Threshold-Free Cluster Enhancement (TFCE). Without being reliant upon hard threshold-based clustering, this method optimizes areas of signal that show spatial contiguity. An algorithm runs though the image, with the aim to better distinguish between signal and noise [49]. After employing the TFCE inference algorithm, the statistical threshold for the resulting correlation maps was set to $p<0.01$, corrected for multiple comparisons using family-wise error (FWE)-correction to allow for qualitative comparisons. Analyses of covariance (ANCOVAs) were performed for each seed region in both hemispheres and after using TFCE considered significant at $p<0.05$ FWE-corrected. Mean gray matter volume of the seed region, and global gray matter, as well as age (since UHR and HC group differed significantly in terms of mean age) were included as covariates. Considering the relevance of auditory hallucinations in Modinos' et al.

study [31] for SCAs, we included hallucinations and positive symptoms as covariates in the analyses comparing UHR-P and UHR-NP for the auditory and visual network.

Results

Demographics

UHR participants and HC differed significantly in their mean age with HC (M_{age}± SD: 22.1±3.9 years, range 13.9-29.1) being older than UHR participants (M_{age}± SD: 20.2±3.6 years, range 16.2-30.3; t(196)=-3.38, p=0.001, see Table S2), whereas there was no significant difference in mean age between UHR-P compared to UHR-NP (p=0.159, see Table 1). Both comparisons did not reveal any differences in gender distribution (UHR: 77 males/ 56 females, HC: 40 males/ 25 females, p=0.624; UHR-P: 29 males / 22 females, UHR-NP: 48 males/ 34 females, p=0.849). Median time to transition for the UHR-P group was 230 days (range 6-3537 days). Positive psychotic symptoms, indexed on the BPRS-psychotic subscale [41] (p=0.554), and negative psychotic symptoms, assessed with the SANS [42] (p=0.058), did not differ between the groups. There were no significant differences between UHR-P and UHR-NP on CAARMS subscales (Disorders of Thought Content, Perceptual Abnormalities, Conceptual Disorganisation) (see Table 1).

Whole-brain patterns of structural covariance in UHR and HC participants

As anticipated based on past studies, seed-based statistical parametric structural covariance mapping of the DMN, SN, ECN, visual, auditory, motor, speech and

semantic network both for UHR and HC participants mirrored canonical intrinsic connectivity [46] and structural covariance [32] networks (see Figure 1).

ANCOVAs comparing UHR and HC participants

ANCOVAs, with mean seed gray matter intensity, age and global gray matter volume of each seed region as covariates, revealed reduced structural covariance in the DMN between the right angular gyrus and the right posterior cingulate (k=1419, 6 -45 21) and left orbitofrontal cortex (k=1224, -26 32 -5) for UHR participants compared to HC (see Figure S1), and increased structural covariance in the motor network between the left precentral gyrus and left subcallosal cortex (k=1153, -3 16 -11) and paracingulate gyrus (k=1090, -2 44 -6) (see Figure S3) and for the additional seed analysis in the ECN between the right inferior parietal lobule and the paracingulate gyrus (k=1537, -9 41 28 & k=1214, -10 34 4) (see Figure 2/S2 & Table S3).

ANCOVAs comparing UHR-P with UHR-NP and HC

ANCOVAs, with mean seed gray matter intensity, age and global gray matter volume of each seed region as covariates, revealed increased structural covariance in the SN between the left fronto-insular cortex and the right occipital pole and right superior parietal lobule (2 -96 -17, k=1422 & 4 -76 34, k=1371) (see Figure S4), auditory network between the seed region in the right hemisphere with the left Heschl's gyrus (-26 – 25 12, k=1890) and right ACC (6 45 15, k=1539) (see Figure S6), and motor network between the left precentral gyrus and left superior and inferior and right

middle temporal gyrus (-12 30 39, k=1777; -44 38 6, k=1412 & 30 33 28, k=1609) (see Figure S7), and decreased structural covariance in the ECN between the right dlPFC and right precentral gyrus (54 -1 42, k=1656) (see Figure S5) for UHR participants who transitioned compared to those who did not (see Figure 2). Increased structural covariance was observed when comparing UHR-P with HC individuals only in the auditory network between the right Heschl's gyrus and the superior and inferior frontal gyrus (-12 26 46, k=2146 & -42 35 10, k=1519).

Influence of positive symptoms

In order to account for the potential influence of positive symptoms and specifically hallucinations, additional ANCOVAs were performed for both the visual and auditory network with BPRS positive symptom and hallucination subscale as a fourth covariate, respectively, for the UHR-P vs UHR-NP comparison. The two clusters previously detected within the auditory network were replicated, and an additional cluster in the medial prefrontal cortex emerged with positive symptoms subscale score (see Table S3).

Discussion

This study characterised whole-brain structural covariance patterns of eight large-scale networks in a sample of participants at clinical high risk for psychosis compared to healthy individuals. Seed-based statistical parametric structural covariance mapping for the DMN, SN, ECN, visual, auditory, motor, speech and semantic networks both for UHR and HC participants revealed structural covariance between

brain areas that represent large-scale functional networks [32]. Reduced structural covariance was observed in the UHR sample compared to HC for the DMN, and increased covariance in the motor network and ECN. Those who transitioned to psychosis showed increased structural covariance within the SN, auditory and motor network, and decreased covariance within the ECN compared to those who did not. One of the most replicated neuroimaging findings in schizophrenia, that of frontal volumetric abnormalities (found in both schizophrenia patients [1] and UHR participants [4, 10]), was reflected in abnormalities of structural covariance between the precentral and subcallosal cortex and paracingulate gyrus within the motor network, and between the inferior parietal lobule and frontal areas such as the paracingulate gyrus in the ECN in terms of increased connectivity in UHR individuals, and decreased connectivity with the orbitofrontal cortex within the DMN. These frontal abnormalities were further confirmed when comparing UHR-P and UHR-NP individuals in the ECN between the dlPFC and precentral gyrus and in the motor network between the precentral gyrus and frontal gyri.

Insula alterations [11] were present on the network level in the SN between the fronto-insular cortex and occipital and parietal areas, with an increased connectivity within the SN for those who transitioned to psychosis compared to those who did not, confirming an involvement of the SN [18]. The subtle alterations of the SN that we detected, were however, not present when comparing UHR individuals with HC, suggesting that changes may not generally be responsible for producing subthreshold symptoms, but that they may play a role in distinguishing between those who are going to make a transition and those who are not.

Our findings of altered structural covariance in the DMN - specifically between angular gyrus and PCC and orbitofrontal cortex - are in line with altered functional connectivity in DMN areas in individuals with high genetic loading [21, 22]. Taken together with our findings, this indicates that DMN alterations are associated with risk for psychosis generally rather than being predictive of transition.

One possible explanation for the subtle hyper-connectivity in the auditory network in those individuals who transitioned to psychosis in our UHR sample is the presence of auditory hallucinations. Strikingly, no such hyper-connectivity was discovered when comparing the entire UHR group with HC, however, hyper-connectivity was amplified when comparing those who transitioned with HC. This group difference vanished for the SN and ECN, and motor network when comparing UHR-P with HC, instead of UHR-NP. An alternative explanation against the implicit assumption that brain abnormalities of UHR-NP are located intermediate between UHR-P and HC is the notion that even though UHR-NP individuals display similar symptomatic and/or trait features to UHR individuals who eventually become psychotic, the former hold a certain resilience against transition, and may therefore be distinct to UHR-P individuals. This is supported by the finding of thinning in UHR-P and thickening in UHR-NP of the ACC relative to HC [50].

Because we were primarily interested in three networks associated with psychotic disorders (DMN, SN & ECN), we selected additional seeds to confirm our original

analyses. However, alterations of the DMN could not be replicated with the additional seeds, and one additional seed for the ECN produced a significant difference between UHR individuals and HC that was not shown with the original seed. Although we hypothesized alterations within this network, this underlines the importance of caution in interpreting multiple comparisons. Whereas subtle changes in brain connectivity in these networks are plausible in this cohort, it might be that these findings become non-significant once corrected for multiple comparisons in a multivariate seed analysis. These findings will therefore need to be replicated in other datasets.

There were several limitations to this study. Because of our intention to characterize multiple large-scale networks, we applied individually stringent thresholds to both within- and between-group analyses. While we considered this appropriate and similar to other studies of structural covariance networks, replication of our findings will be important, especially with regard to the aforementioned issue of multiple comparisons at the network level. The alterations observed, albeit discrete, appear to be robust findings, as we controlled for the effect of global gray matter volume, and age as nuisance factors. This last variable could have a significant impact, since brain anatomy experiences extensive changes during adolescence, e.g. decreases in gray matter volume or synaptic pruning [29] – however it seems unlikely that the detected group differences are accounted for by age.

Similar to other recent studies, we have interpreted structural covariance findings in accordance with other measures of structural and functional brain connectivity. Although the observed correspondence among these measures is highly anatomically plausible, multimodal imaging assessments that combine structural and functional MRI and DTI will be increasingly relevant in order to advance this line of enquiry [51]. Another limitation is the cross-sectional design of our study. We were able to determine transition to psychosis status with some confidence, because we followed our sample for an extended period of 13 years. However, future research should focus on longitudinal outcome evaluation by relating network level structural covariance to each other over time, in order to see if symptom progression and actual transition to psychosis directly relate to further and/or more pronounced network alterations. Lastly, images were acquired using a 1.5 T MRI scanner, as opposed to 3T, or developments of even higher field strengths, which have been used in more recent research studies. As a result, spatial resolution of the structural data reported may be compromised; however, the scans of this study were collected almost two decades ago, which allowed for the extended follow-up period.

In conclusion, our findings indicate that network levels of structural covariance are predominantly intact in individuals at ultra-high risk for psychosis. Observed subtle temporal, frontal and parietal alterations are consistent with previous structural and functional connectivity findings in UHR participants and the notion that individuals at clinical risk for psychosis exhibit qualitatively similar but less severe changes than those that have been observed in frank psychosis. Future studies should involve

longitudinal, multimodal imaging assessments to specify structural covariance predictors for transition to psychosis and how these may relate to findings of other brain connectivity techniques.

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Table 1

Demographic information, time to transition and self-report scores at baseline according to transition status

	Transition (n=51)	Non-Transition (n=82)	Test statistic	p-value
Mean age ± SD *(in years)*	19.6±3.6	20.5±3.6	t(131)=-1.416	0.159
Range	13.9-29.1	14.3-28.6		
Gender (m/f)	29/22	48/34	$\chi^2(1)=0.036$	0.849
Mean time to transition ± SD *(in days)*	519.3±666.4	NA	NA	NA
Range	(6-3537)			
BPRS total score	$\tilde{x}=42$	$\tilde{x}=43$	U=1939 Z=-0.592	0.554
BPRS Positive Symptoms Score	$\tilde{x}=8$	$\tilde{x}=8$	U=1822 Z=-1.546	0.252
(*n* = 51 vs 81)				

BPRS Hallucination score (*n* = 51 vs 81)	$\tilde{x}$=2	$\tilde{x}$=2	U=2050.5 Z=-0.075	0.94
SANS total score	$\tilde{x}$=19	$\tilde{x}$=16	U=1682 Z=-1.894	0.058
CAARMS DTC (*n* = 50 vs 81)	$\tilde{x}$=2	$\tilde{x}$=2	U=1668.5 Z=-1.772	0.076
CAARMS PA (*n* = 50 vs 81)	$\tilde{x}$=2	$\tilde{x}$=2	U=1838.5 Z=-0.915	0.360
CAARMS CD (*n* = 50 vs 81)	$\tilde{x}$=2	$\tilde{x}$=2	U=1863 Z=-0.823	0.41

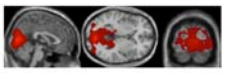
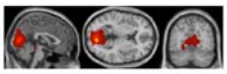
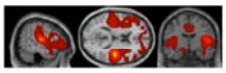
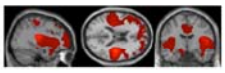
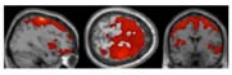
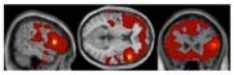
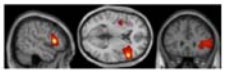
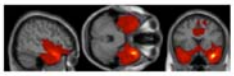
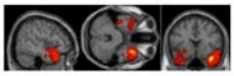
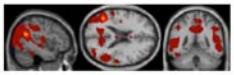
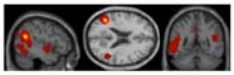
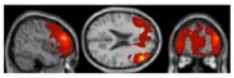
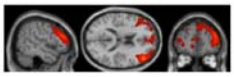
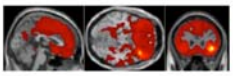
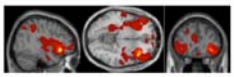
Notes. n=sample size, SD=standard deviation, m=male, f=female, NA=not applicable, BPRS=Brief Psychiatric Rating Scale, SANS=Scale for the Assessment of Negative Symptoms, CAARMS=Comprehensive Assessment of At-Risk Mental States, DTC=Disorders of Thought Content, PA=Perceptual Abnormalities, CD=Conceptual Disorganisation.

Figure 1. Patterns of structural covariance in ultra-high risk compared to healthy control participants for the visual, auditory, motor, speech, semantic, default-mode, salience and executive-control network.

Figure 2. Axial slices of (A) reduced structural covariance (SC) in the default-mode network between the right angular gyrus and right posterior cingulate and left orbitofrontal cortex in ultra-high risk (UHR) participants compared to healthy controls (HC), (B) increased SC in the executive control network (ECN) between the right inferior parietal lobule and the left paracingulate cortex in UHR individuals compared to HC, (C) increased SC in the motor network between the left precentral gyrus and left subcallosal cortex and paracingulate gyrus in UHR individuals compared to HC,

(D) increased SC in the salience network between the left fronto-insular cortex and right occipital pole and superior parietal lobule for those who transitioned (UHR-P) compared to those who did not (UHR-NP), (E) decreased SC in the ECN between the right dorsolateral prefrontal cortex and right precentral gyrus for UHR-P compared to UHR-NP (F) increased SC in the auditory network between the right and left Heschl's gyrus and right anterior cingulate cortex for UHR-P compared to UHR-NP, (G) increased SC in the motor network between the left precentral gyrus and left superior and inferior and right middle frontal gyrus for UHR-P compared to UHR-NP.

Fig. 1

Network Seed MNI Coordinates	Covariance Maps UHR	 HC	Cluster Size UHR	 HC	Brain Area
Visual Network Calcarine Sulcus 9 -81 7			29693	14808	Right Intracalcarine Cortex
Auditory Network Heschl's Gyrus 46 -18 10			101122	8682 5969	Right Heschl's Gyrus
Motor Network Precentral Gyrus 28 -16 66			71830 428 150 26, 32	1967 - - -	Right Precentral Gyrus Left Precuneus Left Supramarginal Gyrus Left Frontal Pole
Speech Network Inferior Frontal Gyrus 50 18 7			118286	5844 2170	Right Inferior Frontal Gyrus Left Insular Cortex
Semantic Network Temporal Pole 38 10 -28			106658	6842	Right Temporal Pole
Default-Mode Network Angular Gyrus 46 -59 23			29693	14808	Right Intracalcarine Cortex
Executive Control Network dlPFC 44 36 20			64061 -	20818 64	Right Frontal Pole Left Paracingulate Gyrus
Salience Network Frontoinsular Cortex 38 26 -10			177293 - - - - - - -	15266 15283 22168 857, 164, 62 56 86 27 94	Right Orbitofrontal Cortex Left Orbitofrontal Cortex Left Posterior Cingulate Cortex Left Frontal Pole Left Superior Parietal Lobule Right Middle Temporal Gyrus Right Frontal Pole Right Parahippocampal Gyrus Right Lateral Occipital Cortex

A more stringent family-wise error (FWE)- and threshold-free cluster enhancement (TFCE)- corrected p-value of *0.01* has been chosen to demonstrate only most statistically significant clusters (as opposed to FWE- and TFCE-corrected p-values of 0.05 for group comparisons).

Fig. 2