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Aberrant Temporal Connectivity in Persons at Clinical High Risk for Psychosis

Tiziano Colibazzi, MD[1], **Zhen Yang, Ph.D**[2], **Guillermo Horga, MD**[1], **Yan Chao-Gan, Ph.D.**[3], **Cheryl M Corcoran, M.D.**[1], **Kristin Klahr, Ph.D.**[1], **Gary Brucato, Ph.D**[1], **Ragy Girgis, MD**[1], **Anissa Abi-Dargham, MD**[1], **Michael P. Milham, MD, PhD.**[2,*], and **Bradley S. Peterson, MD**[4,*]

[1]Department of Psychiatry, The New York State Psychiatric Institute, Columbia College of Physicians and Surgeons, New York, NY, USA

[2]Child Mind Institute, New York, NY, USA

[3]Key Laboratory of Behavioral Science and Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

[4]Institute for the Developing Mind, Children's Hospital Los Angeles and the Keck School of Medicine, University of Southern California

Abstract

Background—Schizophrenia, a neurodevelopmental disorder, involves abnormalities in functional connectivity (FC) across distributed neural networks, which are thought to antedate the emergence of psychosis. In a cohort of adolescents and young adults at clinical high risk (CHR) for psychosis, we applied data-driven approaches to resting-state fMRI data so as to systematically characterize FC abnormalities during this period and determine whether these abnormalities are associated with psychosis risk and severity of psychotic symptoms.

Methods—Fifty-one CHR participants and 47 matched healthy controls (HCs) were included in our analyses. Twelve of these CHR participants developed psychosis within 3.9 years. We estimated one multivariate measure of FC and studied its relationship to CHR status, conversion to psychosis and positive symptom severity.

Results—Multivariate analyses revealed between-group differences in whole-brain connectivity patterns of bilateral temporal areas, mostly affecting their functional connections to the thalamus. Further, more severe positive symptoms were associated with greater connectivity abnormalities in the anterior cingulate and frontal cortex.

Address for Correspondence: Tiziano Colibazzi, MD, College of Physicians and Surgeons and New York State Psychiatric Institute, Division of Translational Imaging, Office 6104, Unit 74, 1051 Riverside Drive, New York NY 10032. tc2237@columbia.edu.

[*]Bradley S. Peterson and Michael P. Milham equally contributed as senior authors in this study.

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Conclusions—Our study demonstrates that the well-established FC abnormalities of the thalamus and temporal areas observed in schizophrenia are also present in the CHR period, with aberrant connectivity of the temporal cortex most associated with psychosis risk.

Keywords

temporal cortex; prodrome; clinical high-risk; connectivity; connectome; thalamus

INTRODUCTION

Schizophrenia is increasingly conceptualized as a brain disorder of abnormal anatomical (1–3) and functional connectivity(4–8). First, studies of functional connectivity have observed hyperconnectivity in the prefrontal cortex (9) and in the default mode network(10), though hypoconnectivity appears to be more frequently reported (4). Second, disruptions in connectivity affect the general architecture of brain networks in schizophrenia. Findings of reduced distal connectivity and enhanced local connectivity between cognitive control networks (11) and disruptions of topological properties with decreased hub dominance (12) both point to impaired coordination among different networks and to an organizational rearrangement within each network. Moreover, available studies in patients with psychotic illness suggest the existence of network-level dysconnectivity (13) involving both the frontoparietal (14) and the frontotemporal (15) networks. Reductions in frontoparietal connectivity have been found in psychotic illness (16), in addition to hypoconnectivity within fronto-thalamic circuits (17).

Though these studies are informative, insights into the period of clinical high risk (CHR) for psychosis are critical in order to understand the pathophysiology of psychosis. Though CHR cohorts are fairly heterogeneous, a significant portion of these individuals transitions to psychosis within a few years (18)(19)(20)(21). Consequently, the investigation of the CHR period could help us disentangle truly pathogenic abnormalities from the effects of chronic illness and its treatments.

Despite these advantages, few studies have investigated functional connectivity during the period of clinical high risk (CHR) for psychosis (22, 23) (24).

Findings similar to those reported in schizophrenia (10) have been shown in the CHR period, with reports of hyperconnectivity within default network regions (23) and of loss of coordination between task positive and default mode networks (25). Moreover, dysconnectivity appears to affect language-related regions as suggested by the observation of reduced connectivity in CHR individuals between the frontal cortex and Broca’s area (22).

Similar to studies in individuals with schizophrenia (26, 27) (28) and in their first-degree relatives (29), CHR individuals also exhibit dysconnectivity within the cortico-striatal-thalamo-cortical networks, specifically hypoconnectivity between the dorsal caudate and the right dorsolateral prefrontal cortex (DLPFC), rostral medial prefrontal cortex and thalamus (30). More recent findings of thalamo-cortical dysconnectivity in CHR individuals, especially in those who later convert to psychosis (24), further corroborate the notion that

abnormalities of functional connectivity in cortico-striatal-thalamic cortical loops play an important role in the pathogenesis of psychotic illness.

Taken together, these findings suggest that circuit-level functional dysconnectivity could be a risk phenotype for psychosis. Such network-level dysconnectivity has been hypothesized to be the common final pathway through which diverse causal influences may lead to illness (31).

The majority of the studies in CHR individuals to date have used hypothesis-driven approaches limiting the analyses to preselected regions of interest (ROIs) or seeds. These ROI-based approaches offer several statistical advantages, though they may present problems of interpretability, especially when investigating distributed relationships among brain regions, such as those captured by measures of functional connectivity. Other studies of both schizophrenia (32), the CHR phase (33) (34) and similar cohorts with psychosis spectrum symptoms (35) have applied data-driven approaches to the analysis of structural and functional imaging data. These data-driven methods can complement and extend hypothesis-driven methods because of their potential to assess whole-brain measures of functional connectivity in an unbiased manner, and to allow for data-driven selection of ROIs that can be subsequently investigated with more traditional seed-based analyses.

In this study, we aimed to characterize intrinsic functional connectivity in CHR individuals using well–established data-driven metrics of functional connectivity, in order to capture regional, and whole-brain functional interactions between brain regions. We employed a multivariate approach (multivariate distance matrix regression or MDMR) to evaluate simultaneously the contribution of all the possible functional connections of a given brain region to risk-status and symptoms severity in CHR individuals. This multivariate approach, already successfully applied to the study of psychosis (35), has the advantage of providing a comprehensive and unbiased characterization of the totality of functional connections in the brain, without requiring the high number of statistical tests inherent in the frequently used massive univariate approaches.

Based on previous studies in schizophrenia (17, 26) and in clinical high-risk (CHR) cohorts (24), we predicted that CHR individuals would have abnormal functional connectivity involving subcortical regions, in particular the thalamus, and multimodal association cortical areas, belonging to the frontoparietal cortical network, chiefly the DLPFC, in addition to temporal and parietal regions (32). Specifically, we expected an increase in functional connectivity between temporal areas and the thalamus consistent with previous findings in schizophrenia by Anticevic (26), showing increased thalamic connectivity with a set of lateral cortices (including the superior temporal gyrus) and with more recent findings of hyper- and hypoconnectivity of the thalamus with several cortical areas in individuals with psychotic illness (17). This hypothesis is also in line with reports of disrupted structural thalamo-cortical connectivity in CHR subjects and individuals with first episode psychosis (3). Moreover, recent evidence from animal models of schizophrenia points to a specific alteration of thalamic input to the auditory cortex subsequent to elevation in dopamine receptor levels in the thalamus (36) (37).

Finally we predicted that this dysconnectivity would be correlated with severity of symptoms in independently conducted, data-driven analyses.

METHODS

Participants

Our original cohort included 61 CHR individuals enrolled in the COPE (Center of Prevention and Evaluation) clinic at the New York State Psychiatric Institute. Baseline resting state imaging data and clinical baseline and follow-up data were available. Out of the available resting state scans (55), four CHR individuals (among whom two were converters) were excluded as motion outliers (either mean frame-wise displacement (FD power) outside of three standard deviation or over 50% frames with FD>0.2mm). Our final sample for the analyses consisted of 51 CHR individuals (21.0 ±3.78 years, 37males/14 females) and 47 HCs (21.6 ± 3.84 years, 27 males/20 females). Risk for psychosis was assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS)(21), CHR participants and HCs were matched for minority status (here defined as being non-Caucasian) and did not differ in age, gender, or in-scanner head motion (all $p > 0.05$; see also Table 1).

Eight CHR individuals were on antipsychotic medication at the time of scanning (including 3 converters). Functional outcome was measured at baseline and at the last follow-up (mean time to last follow-up = 17.37 ± 15.0 months) using two subscales of the Global Functioning Scale: Social (GSF:S) and Role (GSF:R)(38). Scores ≤6 indicate poor outcome and scores >6 indicate good outcome(39). Further details on this CHR cohort are available in the supplementary material.

MRI Data

Acquisition For details of the MRI data acquisition and preprocessing, refer to the supplementary material. Briefly, we acquired images on a GE Signa 3-T whole-body scanner. For RS acquisition, participants were instructed to remain still with their eyes closed and to let their minds wander freely. The total acquisition time for the resting state sequence was 5 minutes and 21 seconds. Imaging data were preprocessed using Configurable Pipeline For The Analysis Of Connectomes (CPAC version 0.3.3, http://fcp-indi.github.io/docs/user/index.html).

Data Analyses

Multivariate approach MDMR identifies voxels where whole-brain connectivity patterns vary significantly with a phenotypic variable of interest (in our case, CHR status or severity of total positive symptoms)(40). The MDMR approach was conducted using the publicly available R package Connectir (connectir.projects.nitrc.org). In order to reduce computational demands, we restrained our MDMR analyses within a group mask including only voxels present in all participants ($3mm^3$ resolution, in MNI152 standard space) and falling within the 25% gray matter tissue prior mask provided by FSL.

For each voxel, the MDMR analysis included: (1) Estimation of the whole-brain FC pattern of this voxel for each participant by calculating the Pearson's correlation coefficient between

the time series of this voxel and that of all other voxels within the group mask; (2) estimation of the spatial similarity (Pearson's correlation) of the whole-brain connectivity pattern between pairs of participants; this yields an n × n correlation matrix, where n is the number of participants (n = 98 for categorical analysis and n = 51 for dimensional analyses); (3) conversion of each Pearson's r into a distance measure using $\sqrt{2} \times (1 - r)$ to produce an n × n distance matrix(41); (4) testing of the extent to which diagnostic status or symptom severity explains the distances of whole-brain connectivity between participants by using the following MDMR models(42):

$$\text{Distance Matrix} = \beta 0 + \beta 1 \times \text{Group} + \beta \mathbf{2} \times \text{Age} + \beta \mathbf{3} \times \text{Sex} + \beta 4 \times \text{Handedness} + \beta 5 \times \text{FD} \quad (1)$$

$$\text{Distance Matrix} = \beta 0 + \beta 1 \times \text{Total Positive Symptoms Score} + \beta \mathbf{2} \times \text{Age} + \beta 3 \times \text{Sex} + \beta 4 \times \text{Handedness} + \beta 5 \times \text{FD} \quad (2)$$

At the group level, we examined the categorical effect of Group (CHR vs. HCs)(model 1) and the dimensional effect of clinical symptoms at baseline within the CHR group (model 2). For model (2), we used the total positive symptoms score from the SOPS (the sum of item P1 through P5 of the positive symptom subscale), as done in previous CHR studies (24). Results were corrected for multiple comparisons using Gaussian Random Field (GRF) theory. We used the Easythresh tool in FSL and the smoothness of the statistical images was estimated automatically through the "smoothest" program in FSL. This effective smoothness is slightly bigger than the applied smoothness kernel (FWHM=8mm) during preprocessing because the pre-smooth image has implicit smoothness(43).

MDMR yields a pseudo-F statistic analogous to the F statistic obtained in ANOVA. The significance of the pseudo-F value for a given voxel is assessed using a permutation test (15,000 permutations) as described in Shehzad(40). We permuted: 1) group membership assignments (CHR, HC) when we compared CHR individuals and controls; and 2) scores of symptom severity when we investigated MDMR-symptom correlations in the CHR group. The resulting p values were converted to Z scores and corrected for multiple comparisons using GRF. The cluster-defining threshold was Z>1.96, which is equivalent to a one-tailed p of 0.025; the corrected cluster-level threshold was p<0.05. Given the exploratory nature of MDMR, previous reports(35) in clinical samples had used more liberal criteria (for instance cluster defining threshold of Z>1.64 and a smaller number of permutations). Here, we chose a higher height threshold in order to be more conservative and improve the interpretability of the results.

MDMR can reveal the presence of a relationship between phenotypic variables and the pattern of whole-brain connectivity. This method, however, does not inform us about the specific connections that drive these brain-phenotype associations. We performed, as follow-up analyses, ROI-based functional connectivity analyses to identify specific connections implicated in the observed MDMR effect by using as seeds regions significant in the MDMR

analyses. At the individual level, the average time-series across all voxels of a given seed ROI was computed and Pearson-correlated (Fisher Z-transformed) with all voxels within the brain.

We carried out univariate analyses in order to identify patterns of FC that significantly differ between the CHR and HC groups. At the group level, the General Linear Model (GLM) implemented in the toolbox for Data Processing & Analysis of Brain Imaging(43–45) (DPABI: www.rfmri.org/dpabi) was used to examine the categorical effect of Group (CHR vs. HCs). Age, gender, handedness, and head motion (mean FD), and global mean of functional connectivity (FC) of the given seed (46) were entered as nuisance covariates in the following model:

$$\mathrm{FC} = \beta 0 + \beta 1 \times \mathrm{Group} + \beta \mathbf{2} \times \mathrm{Age} + \beta \mathbf{3} \times \mathrm{Sex} + \beta \mathbf{4} \times \mathrm{Handedness} + \beta \mathbf{5} \times \mathrm{meanFD} + \beta 6 \times \mathrm{Global\ mean\ \ (of\ FC\ for\ the\ seed\ ROI)}. \quad (3)$$

Results were corrected for multiple comparisons using Gaussian Random Field (GRF) theory. We applied the following thresholds: the cluster-defining threshold was Z > 2.58, which is equivalent to a two-tailed p of 0.01. The corrected cluster-level threshold was p<0.025. The threshold of p < 0.025 was used to account for the number of seed ROIs, which was derived from a threshold value of p = 0.05, Bonferroni-corrected for 2 seeds (0.05/2=0.025).

The minimum number of voxels in a cluster was based on the cluster extent threshold.

Secondary analyses: Medication Effects—In order to rule out the potential confounding contribution of medications, we carried out the same group analyses described above after excluding individuals taking antipsychotic medications at the time of scanning.

Secondary analyses: Conversion Effects—In order to rule out the potential that CHR converters in our sample were driving the group differences observed in the entire CHR group, we carried out the same group analyses described above after excluding the twelve individuals who later developed psychosis (CHR converters).

RESULTS

Clinical Sample

Fourteen participants in this CHR sample eventually developed psychosis within 3.9 years (conversion rate 23%). Functional outcome was measured at baseline and at the last follow-up (mean time to last follow-up = 17.37 ± 15.0 months) using two subscales of the Global Functioning Scale: Social (GSF:S) and Role (GSF:R)(38). Scores ≤6 indicate poor outcome and scores >6 indicate good outcome(39).

At baseline, our cohort was characterized by impairments in role (mean= 5.86 ± 2.2; n= 45; 86.7% of the sample ≤ 6) and social functioning (mean= 5.9 ± 1.4; n= 45; 73.3% of the sample ≤ 6). At last follow-up, impairment in role functioning (mean= 6.28 ± 1.65; n= 39; 48.7% of the sample ≤ 6) and impairment in social functioning (mean = 5.72 ± 3.00; n = 40; 47.5% of the sample ≤ 6) were still observed (Table 2). Our rates of conversion to psychosis, rates of exposure to antipsychotic medications(47–49), and the magnitude of social and role functioning impairments(39) were comparable to those reported in other CHR cohorts (also refer to the supplementary material for further details on our CHR cohort). Four participants converted in less than 1 year, five participants between 1 and 2 years, three participants between 2 and 3 years and two participants between 3 and 4 years. In essence, almost 65% of the converters' subsample converted within 2 years and almost 86% of the converters' subsample converted within 3 years, which is a typical pattern for CHR studies (19).

Functional connectivity associated with CHR for psychosis

MDMR indicated that abnormal brain-wide connectivity of a left hemispheric cluster centered at the temporal lobe (mostly HG) and at the supramarginal gyrus (SMG) was associated with diagnostic status (CHR). Similarly, abnormal brain-wide connectivity of a right hemispheric cluster centered at the MTG was also associated with CHR status (cluster-defining threshold $Z>1.96$; corrected cluster-level threshold $p<0.05$; refer to Table S1). These clusters were used as seeds in the follow-up functional connectivity (FC) analyses and these analyses revealed that, compared with HCs, CHR individuals exhibited higher functional connectivity of the left hemispheric cluster with the thalamus, bilaterally, the right superior frontal gyrus (SFG), including the DLPFC, and the right paracingulate gyrus (Cluster-defining threshold $Z > 2.58$; corrected cluster-level threshold $p<0.025$; refer to Table S1). CHR individuals also exhibited higher functional connectivity of the right hemispheric cluster bilaterally with the thalamus, striatum and midbrain. In addition, we also observed, hypo-connectivity of this seed with the middle and superior portions of the posterior left temporal lobe (Cluster-defining threshold $Z > 2.58$; corrected cluster-level threshold $p<0.025$; refer to Table S1).

Functional connectivity associated with symptom severity

MDMR identified clusters of regions where patterns of whole-brain functional connectivity were significantly related to the severity of positive symptoms (cluster-defining threshold $Z > 1.96$; corrected cluster-level threshold $p < 0.05$)(Fig.3). These clusters included the right and left medial frontal gyri (MFG), the left SFG (including the DLPFC), the left dACC, the right and left amygdala, the right and left the hippocampus and thalamus (bilaterally).

Secondary Analyses: Medication Effects

Our findings for the comparison of CHR subjects with HCs survived after excluding those eight subjects who were on antipsychotic medications at the time of scanning (Fig. S1).

Secondary Analyses: Converters Effects

Our findings for the comparison of CHR subjects with HCs survived after excluding CHR-converters (Fig. S2).

DISCUSSION

We examined functional connectivity (FC) in 51 CHR and 47 HC individuals and found that abnormalities in connectivity within the temporal cortex, thalamus, striatum and midbrain were consistently associated with risk for psychosis.

We observed abnormal patterns of whole-brain connectivity of a left perisylvian and of a right temporal cortical cluster. These clusters included the temporal cortex, bilaterally, (encompassing the primary auditory cortex) and the left supramarginal gyrus, though the differential contributions of these regions to the group effect cannot be determined (50).

Findings from a large number of studies converge on the superior and middle temporal cortex as critical loci of anatomical and functional pathology in schizophrenia (51) and, to a lesser extent, in the CHR period (52). Volumetric reductions of the STG(53) and morphological abnormalities of the planum temporale(54) have long been observed in different phases of the illness, and these same temporal regions have been implicated in the genesis of psychotic symptoms(55).

The posterior STG in particular is part of a network that supports language-related processing in the left hemisphere, in addition to emotion recognition (56)and musicality(57) in the right hemisphere. Aberrant functional connectivity in these critical areas is associated with semantic incoherence in schizophrenia (58) and thought disorder in the CHR period(59). Furthermore, the Heschl's and supramarginal gyri are also components of the perisylvian cortices that lie along the course of the arcuate fasciculus, a key substrate of human language capacity, also affected in schizophrenia (60). The connectivity abnormalities that we observed in these gyri are in line with prior findings further supporting the involvement of language-related circuits in the clinical high-risk phase and with the observation that specific features of speech complexity may predict conversion to psychosis (61).

By conducting seed-based analyses in those cortical regions showing abnormal whole-brain patterns of functional connectivity (Fig1,2), we determined that left perisylvian areas were hyperconnected to the thalamus, the midbrain, the striatum, the anterior cingulate gyrus and the superior frontal cortex. The right middle temporal gyrus was hyperconnected with the thalamus, midbrain and striatum and hypoconnected with the left superior and middle temporal gyri and with the left angular gyrus.

Thalamo-cortical dysconnectivity has been previously reported in schizophrenia (26) and in the clinical high-risk phase (24) and in patients with schizophrenia the thalamus was found to be more strongly connected to a large band of lateral cortex including temporal areas and sensorimotor areas and hypo-connected to frontal areas. Our results are mostly consistent with these findings, because the cortical areas described in these studies include the temporal areas found to be abnormal in our report (Fig.1,2). Our study is however different because it narrows the locus of abnormalities to thalamo-temporal connections. Furthermore, instead of probing the functional connections of the thalamus chosen as an a priori ROI (26), we examined in a more unbiased way the functional connections of those brain regions which demonstrated abnormal brain-wide connectivity profiles, thus relying on a data-driven rather

than a–priori ROI selection. These temporal areas were also more strongly connected to the midbrain and striatum consistent with a large body of literature that also points to the midbrain and the striatum as critical loci of pathology in schizophrenia (62–64) and in the phase of clinical high risk for psychosis (65, 66) (67). Our MDMR-based seed analyses indicated that the right temporal regions had lower connectivity with the left temporal cortices, consistent with findings of interhemispheric functional and anatomical dysconnectivity in schizophrenia (68) (69, 70) and in clinical high risk cohorts (71).

Whole-brain analyses using MDMR have been used in different cohorts including pediatric samples (72), individuals with Attention Deficit/Hyperactivity Disorder (40, 73), cohorts with psychosis-spectrum symptoms (35) as well as depression and post-traumatic stress disorder (74). Compared to classic seed-based analyses, MDMR has the advantage of using information from all voxels in order to identify “hot spots” of dysconnectivity. More recently, this data-driven approach has been used to explore brain-behavior correlations in effort to identify phenotypic domains (75) consistent with more the dimensional diagnostic framework advocated by the Research Domain Criteria (RDoC) initiative(76)

The severity of positive symptoms appeared to be more associated with dysconnectivity in a different cluster of cortical areas than is risk for psychosis, centering predominantly on the cingulate gyrus and frontal cortex rather than on the lateral temporal cortex associated with CHR status.

Though, the differential contributions of the different regions cannot be determined (50), more severe positive symptoms were associated with disrupted brain-wide functional connectivity in the dACC, vACC, and DLPFC in addition to the hippocampus and the amygdala.

This observation is consistent with the presence of anatomical abnormalities of the cingulate gyrus and frontal lobe in the CHR phase of psychotic illness (77) (78) and schizophrenia (79, 80) (81). Our results suggest that in the period of clinical high risk for psychotic illness lateral temporal cortices may play a different role than frontal and cingulate areas, with the former associated with psychosis-risk and the latter with symptom burden. We speculate that this difference could be reflected in different patterns of dysconnectivity. For instance, symptoms could be related to failure of top-down cognitive control on subcortical nodes, in particular the amygdala (82) and hippocampus (83) and in fact, dysconnectivity in cognitive control networks has been shown in a variety of psychotic illnesses (84) (32).

Several limitations need to be considered. First, there is a relatively small absolute number of CHR converters in our sample. Our conversion rate for our sample (23%) however is considered typical of CHR research (47, 49, 85, 86) and similar to the rates observed in a recent meta-analysis (18) and in various consortia, such as the European Prediction Of Psychosis Study (87). Second, the heterogeneous nature of CHR cohorts and their typically small sample sizes carry a risk of incurring in false negatives rather than false positives, thus our choice of a threshold that was not too stringent (yet more conservative than previous studies) for the initial data-driven identification of ROI whose patterns of functional connectivity was associated with CHR status. We acknowledge that as the sample sizes for

such cohorts grow, more stringent corrections can be used. Furthermore, one must keep in mind only liberal thresholds that yield larger clusters can detect significant effects in cases where the true activity pattern is not localized to a discrete anatomical region but it is, on the contrary, more distributed.

Third, our CHR participants were taking medications at the time of scan. However, our rate of exposure to antipsychotic medications and stimulant medications was similar to other CHR cohorts(24). More importantly, our findings remained in analyses that excluded participants taking antipsychotic medications (Fig. S1), suggesting that abnormal connectivity patterns in CHR individuals cannot be accounted for by exposure to antipsychotic medications.

Fourth, a unified correction for the different data-driven measures of functional connectivity, though desirable, is only feasible for much larger sample sizes. We also note that such unified correction may pose problems such as overcorrection because MDMR, Degree Centrality and Voxel Mirrored Homotopic Connectivity are not entirely independent measures.

We also need to emphasize the need for replication of our results, in light of the *post hoc* nature of the MDMR-follow up analyses of functional connectivity (50). Such follow up analyses are not independent from MDMR because they simply interrogate the MDMR-identified voxels in order to understand in what particular way the connectivity pattern of these voxels differs between CHR participants and HCs.

Finally, our analyses do not allow us to specify which area or areas - among those that compose a given cluster- is driving the findings in that cluster or to what proportion such areas contribute to the observed effects relative to one another. Therefore no conclusions can be drawn about any of the specific locations within a given cluster (50). Moreover, we remind the reader that the MDMR follow-up analyses describe the connectivity patterns of the entire cluster rather than that of the individual regions included in the cluster.

In conclusion, our data-driven approach identifies cortical areas such as the temporal cortex and the thalamus as key regions associated with risk for psychosis, whereas symptom severity appears correlated with functional dysconnectivity in cognitive control regions. These findings suggest that temporal dysconnectivity may be a trait-related risk marker for psychotic illness, whereas functional disturbances in the anterior cingulate cortex and in the dorsolateral prefrontal cortex may constitute a more general non-specific state-related marker of concurrent positive symptom severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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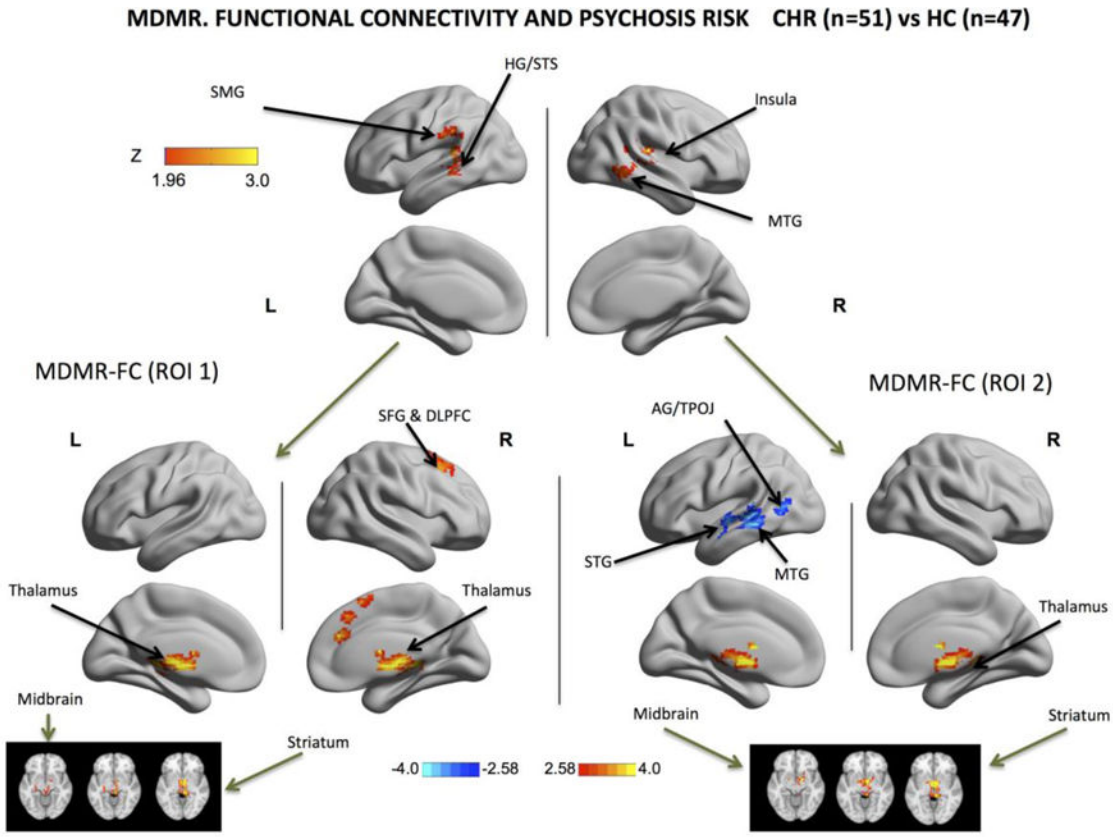

Fig.1. Intrinsic Functional Connectivity Associated with Clinical High Risk (CHR) for Psychosis. MDMR and MDMR-guided functional connectivity analyses

Using Brainnetview, the Z scores of areas exhibiting significant MDMR-related group effects (CHR vs. HCs) were plotted on the surface map. Results for the MDMR (Multivariate Distance Matrix Regression, *Upper Panel*) were GRF-corrected for multiple comparisons: cluster-defining threshold $Z > 1.96$; corrected cluster-level threshold $p < 0.05$ (estimated smoothness of the statistical images in FSL Easythresh: FWHMx=9.9.mm; FWHMy=10.2mm; FWHMz=8.9 mm). MDMR-guided functional connectivity (FC) analyses were conducted using the MDMR-significant regions in the left hemisphere (*Lower Left Panel*) and in the right hemisphere (*Lower Right Panel*) with correction for multiple comparisons. MDMR univariate FC analyses, left cluster: cluster-defining threshold $Z > 2.58$; corrected cluster-level threshold $p<0.025$. The threshold of 0.025 is used to account for the number of seed ROIs, which is derived from a threshold value of $p = 0.05$ Bonferroni-corrected for 2 seeds (0.05/2=0.025); (estimated smoothness of the statistical images in FSL Easythresh: FWHMx= 14.9.mm; FWHMy= 15.2mm; FWHMz=13.8mm). MDMR univariate FC analyses, right cluster: cluster-defining threshold $Z > 2.58$; corrected cluster-level threshold $p<0.025$. The threshold of 0.025 is used to account for the number of seed ROIs, which is derived from a threshold value of $p = 0.05$ Bonferroni-corrected for 2 seeds (0.05/2=0.025);(estimated smoothness of the statistical images in FSL Easythresh: FWHMx=14.5mm; FWHMy= 13.9mm; FWHMz=13.1mm). For MDMR, the warm color indicates the presence and strength of an association between the pattern of whole-brain connections and the diagnostic group membership. For MDMR-guided functional

connectivity, warm colors indicate that the CHR individuals had higher FC than controls and cold colors indicate that CHR individuals had lower FC than controls. These group comparisons show that CHR individuals have different patterns of whole-brain connectivity in the following cortical regions: left superior temporal cortex (including Heschl's gyrus or HG), left superior temporal sulcus, left supramarginal gyrus and left middle temporal gyrus and on the right side mostly right middle temporal gyrus. Seed-based FC analyses of these regions of abnormal whole-brain connectivity in the left hemisphere (*Lower Left Panel*) showed increased connectivity with prefrontal regions, the cingulate cortex, the thalamus and the midbrain. Regions of abnormal brain connectivity in the right hemisphere exhibited, on the other hand, decreased connectivity with the temporal lobe and increased connectivity with the thalamus, the striatum and the midbrain (this is also shown in 3 axial slices at the bottom right and bottom left corners). HG: Heschl's Gyrus; MTG: Middle Temporal Gyrus; SMG: Supramarginal Gyrus; STG: Superior Temporal Gyrus. STS: Superior Temporal Sulcus. ROI 1: Region Of Interest 1 identified by MDMR in the Left Hemisphere and displayed in the upper left half of the figure. ROI 2: Region Of Interest 2 identified by MDMR in the Right Hemisphere and displayed in the upper right half of the figure.

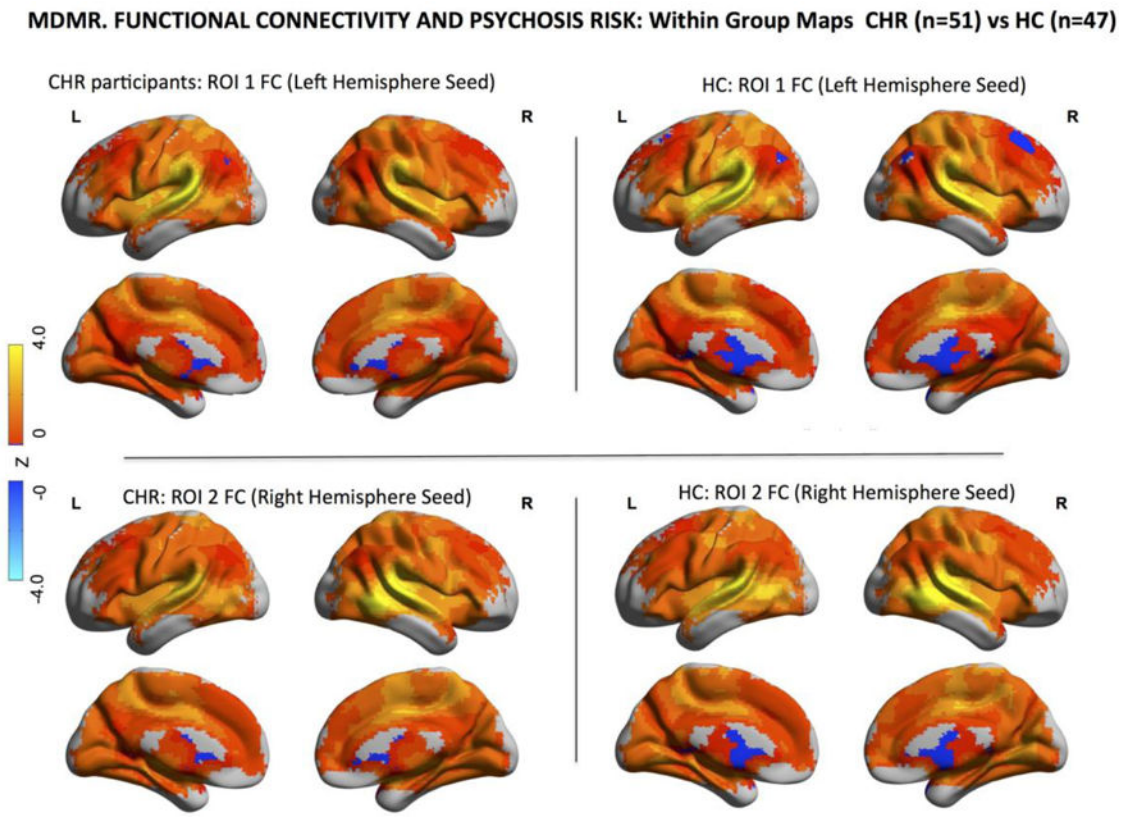

Fig. 2. Intrinsic Functional Connectivity Associated with Clinical High Risk (CHR) for Psychosis

Within-group maps of brain-wide functional connectivity for healthy controls (HCs) and CHR participants for the two ROIs identified by MDMR and displayed in Fig.1. The comparison of these connectivity maps, here displayed separately, for CHR individuals and healthy controls yields the between-group maps displayed in the lower half of Fig. 1 also referred to as MDMR-follow up analyses. For these maps of MDMR-guided functional connectivity, warm colors indicate positive values of functional connectivity and cold colors indicate negative values of functional connectivity between the seed regions (ROI 1 and 2) and other brain areas.

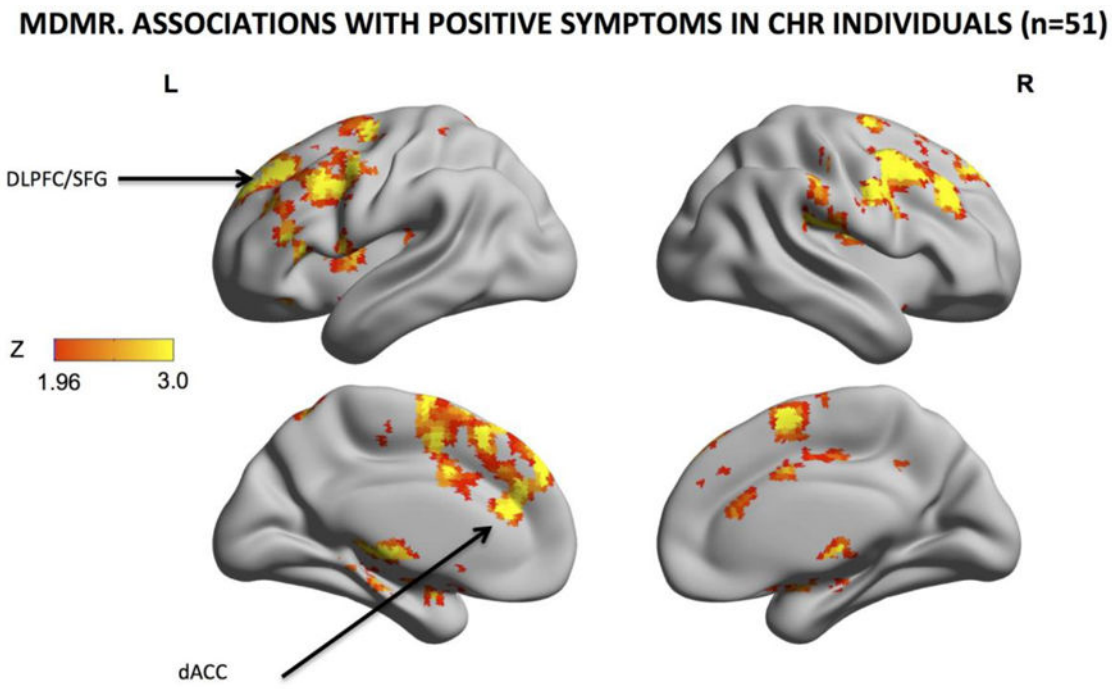

Fig. 3. Intrinsic Functional Connectivity Associated with Positive Symptoms

Z scores of areas whose intrinsic functional connectivity were significantly associated with the severity of positive symptoms were shown on the surface map for (multivariate distance matrix regression or MDMR). The warm color indicates the presence and strength of an association between the pattern of whole-brain connections and the severity of total positive symptoms. Progressively more severe symptoms are associated with whole-brain differences in the pattern of functional connectivity of the dACC, midcingulate cortex, supplementary motor area and mesial superior frontal gyrus. Results were GRF-corrected for multiple comparisons. MDMR: cluster-defining threshold $Z > 1.96$; corrected cluster-level threshold $p < 0.05$; (estimated smoothness of the statistical images in FSL Easythresh: FWHMx= 13.5mm; FWHMy= 13.4mm; FWHMz=11.8mm).

Table 1

Demographic and Clinical Characteristics of Study Participants

Characteristics	CHR participants (n=51)	HCs (n=47)	F/T or Chi-sq	df	p-value
Gender M/F (n)	37/14	27/20	2.462	1	0.117
Age at MRI (years)	21.04 (SD 3.78)	21.64 (SD=3.84)	0.009/−0.776	96	0.440
Education (years)*	13.18 (SD 2.18)	13.74 (SD 2.51)	1.059/−1.158	91	0.250
Head motion (mean FD in mm)	0.12 (SD 0.06)	0.10 (SD 0.06)	0.038/1.00	96	0.316
Minority/Caucasian (n)	35/16	28/19	0.873	1	0.35

*Indicates incomplete data: n=50 for CHR, n=43 for HC.

Table 2

Additional Characteristics of CHR Participants

Characteristics	CHR Participants (n=51)
SIPS Score	
Total Positive Symptoms	12.33 (SD 4.58)
Total Negative Symptoms	14.98 (SD 7.73)
CHR Outcome	
Converted to Psychosis, n (%)	12/51 (23.5%)
Mean Time to Conversion, months	17.05 ± 7.5
Baseline GSF:R *, n=45	5.86 (SD=2.2)
Last GFS:R **, n=39	6.28 (SD=1.65)
Baseline GSF:S *, n=45	5.9 (SD=1.4)
Last GFS:S **, n=40	5.72 (SD=3.00)
Poor Outcome: GFS: ≤ 6, n (%)	19/39 (48.72%)
Poor Outcome: GFS:S ≤ 6, n (%)	19/40 (47.5%)
Medication Type ***, *n*	
Atypical/Typical Antipsychotics	8/0
Mood Stabilizers	1
Antidepressants	17
Stimulants	5
Benzodiazepines	5

* Indicates incomplete data;

** The mean Follow-Up Period (Time to Last Follow Up) was 17.37 months (n=51; SD= 15.0).

*** Information about medication was unavailable for 5 participants