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Structural Network Disorganization in Subjects at Clinical High Risk for Psychosis

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Previous network studies in chronic schizophrenia patients revealed impaired structural organization of the brain's rich-club members, a set of highly interconnected hub regions that play an important integrative role for global brain communication. Moreover, impaired rich-club connectivity has also been found in unaffected siblings of schizophrenia patients, suggesting that abnormal rich-club connectivity is related to familiar, possibly reflecting genetic, vulnerability for schizophrenia. However, no study has yet investigated whether structural rich-club organization is also impaired in individuals with a clinical risk syndrome for psychosis. Diffusion tensor imaging and probabilistic tractography was used to construct structural whole-brain networks in 24 healthy controls and 24 subjects with an at-risk mental state (ARMS). Graph theory was applied to quantify the structural rich-club organization and global network properties. ARMS subjects revealed a significantly altered structural rich-club organization compared with the control group. The disruption of rich-club organization was associated with the severity of negative psychotic symptoms and led to an elevated level of modularity in ARMS subjects. This study shows that abnormal structural rich-club organization is already evident in clinical high-risk subjects for psychosis and further demonstrates the impact of rich-club disorganization on global network communication. Together with previous evidence in chronic schizophrenia patients and unaffected siblings, our findings suggest that abnormal structural rich-club organization may reflect an endophenotypic marker of psychosis.

Key words: psychosis/clinical high risk/structural connectivity/network/rich-club/graph theory

Introduction

Recent network studies propose that connectivity abnormalities in schizophrenia are not solely attributable to changes in local regions and connections, but rather emerge from an aberrant topology of the network as a whole, the connectome of the brain.[1–3] Such graph theoretic mapping techniques have emerged as a very helpful approach to infer complex network properties of the healthy brain[4] and to understand the pathoconnectomic of psychiatric disorders.[5–7] For instance, consistent with reports in chronic schizophrenia patients,[8–13] recent network studies derived from whole-brain graph analyses showed reduced levels of structural global efficiency, reflecting the capacity for network-wide information processing,[4] in non-help-seeking individuals with psychotic experiences[14] and in different populations at increased genetic risk for schizophrenia.[15–18]

One major contribution of graph theory to our understanding of neuropsychiatric diseases has been in highlighting the important role of hubs, which are nodes of the network with an unusually high number or strength of connections.[19] It has been shown that some of these brain hubs tend to be more densely interconnected among themselves than would be expected solely from their high degree, forming together a "rich-club."[20] These members of the brain's rich-club serve as a macroscopic anatomical substrate to cross-link functional networks and thus play an important role in the integration of information between segregated functional domains of the human cortex.[21] The high level of centrality of brain hubs also renders them points of vulnerability that are susceptible to disconnection and dysfunction in psychosis.[6,7,22] Using diffusion tensor imaging (DTI) and resting-state fMRI data, reduced interconnectedness of rich-club regions has been detected in established schizophrenia, which was found to be associated with lower levels of global communication capacity.[9] This study provided novel biological evidence that schizophrenia is characterized by a selective disruption of structural brain connectivity among central brain hubs, potentially leading to reduced communication

capacity and altered functional brain dynamics.[9] Moreover, abnormal rich-club organization is already evident in unaffected siblings of schizophrenia patients if compared with healthy subjects, but less affected than in schizophrenia patients.[23] This study suggested that impaired rich-club connectivity is related to familial, possibly reflecting genetic, vulnerability for schizophrenia.[23]

The present DTI study examined whether structural rich-club organization is also affected in 24 subjects with a clinical high-risk syndrome for psychosis (see[24] for a comprehensive review of the international criteria), in particular with an at-risk mental state (ARMS), compared with 24 healthy controls (HCs). While first-degree relatives of schizophrenia patients have approximately a 10-fold increased risk for developing psychosis over lifetime,[25,26] subjects at clinical high risk have a high probability of transitioning to overt psychosis (mostly schizophrenia spectrum disorders[27]) within a short period (36% within 3 years of presentation).[28] We also assessed global network properties including efficiency and modularity to explore whether they were related to rich-club connectivity across all participants. Although previous research showed that lower levels of structural rich-club connectivity were related to worse overall functioning in chronic schizophrenia patients,[23] no study has yet investigated the impact of abnormal rich-club organization on global functioning and subclinical psychotic symptoms in ARMS subjects. To address this point, we finally tested the relationship of structural rich-club organization to positive and negative attenuated psychotic symptoms, as well as to deficits in global functioning in ARMS subjects. Our first hypothesis was that ARMS subjects would reveal aberrant rich-club organization compared with HCs and that this disruption would be associated with abnormal global network properties. Secondly, we hypothesized a negative relationship between the level of rich-club organization and the severity of attenuated psychotic symptoms and impairments in global functioning in ARMS subjects.

Materials and Methods

Participants

We recruited 24 HCs and 28 ARMS subjects in our specialized clinic for the early detection of psychosis at the Department of Psychiatry, University of Basel (UPK), Switzerland. All participants provided written informed consent, and the study had research ethics committee permission. We assessed subjects using the "Basel Screening Instrument for Psychosis" (BSIP),[29] the Brief Psychiatric Rating Scale (BPRS),[30] the Scale for the Assessment of Negative Symptoms (SANS),[31] and the Global Assessment of Functioning (GAF). We additionally obtained current and previous psychotropic medication, as well as nicotine and illegal drug consumption, by using a semistructured interview (www.eppic.org.au). These exclusion criteria were applied to all groups: history of previous psychotic disorder; psychotic symptomatology secondary to an organic disorder; substance abuse according to ICD-10 research criteria; psychotic symptomatology associated with an bipolar disorder or major depression or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and IQ less than 70.[32]

According to the Personal Assessment and Crisis Evaluation (PACE)[33] and the international standard criteria,[24] inclusion for an ARMS required one or more of the following: (*a*) attenuated psychotic-like symptoms, (*b*) brief limited intermittent psychotic symptoms (BLIPS), or (*c*) a first- or second-degree relative with a psychotic disorder plus at least 2 further risk factors for or indicators of beginning psychosis according to the BSIP screening instrument, such as deterioration in social functioning. Inclusion because of attenuated psychotic symptoms required that change in mental state had to be present at least several times a week and for more than 1 week (a score of 2 or 3 on the BPRS hallucination item, or 3 or 4 on BPRS items for unusual thought content or suspiciousness). Inclusion because of BLIPS required scores of 4 or above on the hallucination item, or 5 or above on the unusual thought content, suspiciousness, or conceptual disorganization items of the BPRS, with each symptom lasting less than 1 week before resolving spontaneously. After the baseline assessment, the ARMS subjects were followed up clinically and received standard psychiatric case management. Five ARMS individuals have transited to psychosis. All ARMS individuals were antipsychotic-naïve and 11 received low-dose antidepressants.

DTI Data Acquisition and Preprocessing

Details of DTI data acquisition and preprocessing steps are described in the supplementary material.

Weighted Connectome Reconstruction

See supplementary figure 1 for an overview of the analytical workflow.

Network Node Definition. Freesurfer software[34] was applied to the individual T1 images to parcellate the brain surface into 68 cortical and 14 subcortical regions (41 per hemisphere), as previously done.[9,20] The 82 segmented regions (see supplementary table 1) for each participant were then coregistered to the individual DTI reference image with $b = 0\,\mathrm{s/mm^2}$.

Tractography-Based Structural Connections. We used the output of a probabilistic tractography algorithm to define the weights of the connections, building a weighted network. Probabilistic tractography methods probe the fiber orientation probability distributions at each voxel, assessing the likelihood of a fiber following a particular path given the diffusion data. Advantages of this method

over the deterministic method include the ability to explicitly represent uncertainty in the data[35] and that it can more reliably reconstruct crossing fibers.[36] Probabilistic tractography was carried out using bedpostX/probtrackX.[35] BedpostX uses Monte Carlo Markov chain sampling to estimate the diffusion parameters at each voxel and also calculates the necessary parameters for probabilistic tractography. The probabilistic tractography (probtrackX) was applied by sampling 5000 streamline fibers per voxel, thus for each region (node hereafter), 5000 × n fibers were sampled, where n is the number of voxels in the node. Results from the probabilistic tractography algorithm are dependent on the seeding position. This implies that the connectivity index calculated from node i to j is not the same as the one from j to i. However, these are highly correlated across the brain regions for all subjects (median R = .86, 95% confidence interval = [0.71; 0.94]). We therefore followed previous authors[37,38] and defined the unidirectional connectivity probability P_{ij} between node i and j by averaging these 2 probabilities. However, the size of a node may influence the fiber selection procedure: bigger seed regions would have more voxels where streamlines would be started, and bigger target regions may have a higher probability of being touched by one of the fiber streamlines. To control for this effect, the number of streamlines between node i and j was normalized by the product of the voxel number of node i and j.

Weighted Rich-Club Effect

The rich-club phenomenon in networks alludes to the tendency of the highly connected nodes to establish more or stronger links among themselves than randomly expected.[39,40] In brief, the weighted rich-club coefficient $\Phi^w(r)$ is computed as the sum of the weights of the subset of connections $E_{>r}$ of the nodes with a richness factor $>r$ in the network divided by the sum of the set of the strongest $E_{>r}$ connections in the total network.[40] Furthermore, to assess the actual presence of the weighted rich-club phenomenon, discounted of random expectations, $\Phi^w(r)$ must be compared with the averaged rich-club curve $\Phi^w_{\text{random}}(r)$ of a (set of) comparable random network(s) to determine the extent to which empirically observed connection density between rich-club nodes exceeds that predicted by a random null model.[39,40] In this study, $\Phi^w_{\text{random}}(r)$ was computed for each level of r by averaging the rich-club coefficient over 1000 random networks, in which the degree and strength distributions were preserved.[41] As such, this normalized rich-club value describes how much the network organization departs from the null model, controlling for the level of connectivity, which might be subject-specific. A normalized coefficient $\Phi^w_{\text{norm}}(r)$ (given as the ratio $\Phi^w(r) / \Phi^w_{\text{random}}(r)$) of >1 over a range of r suggests the existence of rich-club organization in a network.[40]

In this study, r was defined as the node strength (computed as the sum of the weights of the node's connections). We were interested in looking at configurational aspects of the brain network, or the way connections are organized in the network. That meant we were not looking at differences introduced by the absolute level of connectivity across subjects. To further control for a global difference in the level of connectivity between groups (ie, one group having stronger connections across the whole brain), we therefore computed Φ^w_{norm} as a function of percentiles of the node strength for each subject, ranging from 5% to 95% (rich-club level r). In other words, we computed Φ^w_{norm} for each subject looking at the tendency of the network to concentrate its strongest connections in the X percentile of most connected regions. This ensured that irrespective if one subject had an overall much greater connectivity than another one, we would still be comparing whether their top X hubs were concentrating the stronger connections.

Statistical Analysis of Rich-Club Organization

First, 2-tailed Wilcoxon rank-sum tests in Matlab (mathworks.com) were used to verify the existence of rich-club organization in each group, where $\Phi^w_{\text{norm}}(r)$ was significantly larger than zero (P value corrected for the number of rich-club levels, ie, 19). Group differences in $\Phi^w_{\text{norm}}(r)$ were explored using permutation testing (10 000) (P value corrected for the number of rich-club levels). To further test for group differences across different rich-club levels, permutation testing was also performed on the area under the rich-club curve (above 1).

Second, rich-club regions were then defined by selecting for each control subject the top 15% nodes, given their node strengths. This decision was based on the permutation test revealing that the group difference in $\Phi^w_{\text{norm}}(r)$ was most pronounced at the 85% level. This is in line with previous studies defining the top 12% as rich-club regions, given their node degree.[9,20] Only those nodes evident in 85% of HCs were finally selected as rich-club regions. Accordingly, edges were classified into "rich-club connections," being those edges that link members of the rich-club; "feeder connections," which are the edges that link rich-club nodes to peripheral nodes; and "local connections," being those edges that interconnect peripheral nodes. Permutation testing was then used to test for group differences between HCs and the ARMS sample.

Modularity, Efficiency, and Clustering

We also examined the characterization of community (module) structure in the network, meaning the appearance of densely connected groups of nodes, with only sparser connections between groups[42] and global efficiency. Furthermore, we explored local efficiency and clustering (the level of local connectedness of a node) of the

rich-club regions. All metrics were computed using the Brain Connectivity Toolbox[41] based on the individually weighted networks and normalized with the same metrics of a set of random networks ($n = 1000$). Group differences in these graph metrics between HCs and ARMS subjects as a whole group were examined using permutation tests (10 000). Exploratory Pearson correlations were performed to explore the relationships between participants' rich-club organization (across rich-club levels, as indexed by the area under the curve) and global and local network metrics.

Relationship Between Rich-Club Organization and Clinical Features

In ARMS subjects, we tested for potential relationships between the level of rich-club organization and positive (sum of BPRS items: 9 [suspiciousness], 10 [hallucinations], 11 [unusual thought content], and 15 [conceptual disorganization]) and negative (SANS total score) symptoms, as well as global functioning (GAF scores) using Pearson correlations. Findings from the correlational analyses in ARMS subjects are corrected for the total number of performed tests ($P < .05/3$).

Across all participants, we further tested for relationships between rich-club organization, global network metrics, and global functioning using Pearson correlations. Correlation analyses across all participants are also corrected for the number of performed tests ($P < .05/3$).

Results

Demographical and Clinical Features

The 2 groups did not differ in age, handedness, education, premorbid IQ, and cigarette, alcohol, or cannabis consumption, but they differed in gender (table 1). As groups differed in gender, this variable was added as a covariate for all group comparisons of network measures.

Rich-Club Organization

A rich-club organization in the structural network was detected in both groups, ie, normalized rich-club coefficient (Φ^{w}_{norm}) > 1 over a range of r; the rich-club regime ranged from $r = 40$ to $r = 95$ in HCs (Ps < .0001) and from $r = 55$ to $r = 90$ in ARMS subjects (Ps < .0014) (figure 1). Compared with HCs, ARMS subjects revealed a significantly reduced Φ^{w}_{norm} at level 85 ($P = .0251$, corrected for the number of rich-club levels). The area under the rich-club curve was also significantly reduced in ARMS subjects compared with HCs ($P = .0120$), reflecting a lower tendency for the strongest connections to be shared among the hubs of the brain in these subjects.

The rich-club comprised 8 regions, including the bilateral putamen, pallidum, accumbens, and the left caudate and amygdala (figure 2A). We found that ARMS subjects showed significantly reduced mean strength of rich-club connections ($P = .0207$, corrected for the number of connections) compared with HCs (figure 2B), whereas no group difference in the strength of feeder connections was found ($P = .9382$) (figure 2C). Of note, no volumetric group differences were found in rich-club regions (supplementary table 2). Furthermore, there was a statistical trend for increased strength of local connections in ARMS subjects ($P = .0549$) compared with HCs (figure 2D).

Modularity, Efficiency, and Clustering

Structural networks of ARMS subjects revealed an elevated level of modularity compared with HCs ($P = .0272$) (figure 3A). Correcting for the area under the rich-club curve, this group effect was no longer evident ($P = .1313$). Across all participants, we found a negative correlation between the area under the rich-club curve and modularity ($r = -.385$, $P = .007$) (figure 3B). Groups did not differ in global efficiency ($P = .2613$).

Table 1. Clinical and Demographic Characteristics of the Study Sample

	HC ($n = 24$)	ARMS Group ($n = 24$)	Group Statistics
Age (years, mean ± *SD*)	27.75 ± 4.59	25.42 ± 6.74	$t_{46} = 1.400$; $P = .170$
Gender (female/male)	14/10	6/18	$\chi^2 = 5.486$; $P = .019$
Handedness (right)	22	22	$\chi^2 = 0.000$; $P = 1$
Education (years, mean ± *SD*)	15.38 ± 2.92	15.04 ± 3.39	$t_{46} = 0.365$; $P = .717$
Premorbid IQ (MWT-B, mean ± *SD*)	120 ± 11.06	115 ± 14.27	$t_{46} = 1.187$; $P = .242$
Cigarettes smoked per day (mean ± *SD*)	4.08 ± 7.01	6.00 ± 8.20	$t_{46} = -0.871$; $P = .389$
Alcohol consumption (no/moderate/uncontrolled)	1/21/2	4/18/2	$\chi^2 = 2.031$; $P = .362$
Number of subjects consuming cannabis	4	5	$\chi^2 = 0.000$; $P = 1$
GAF total score (mean ± *SD*)	88.63 ± 4.39	68.75 ± 11.8	$t_{46} = 7.733$; $P < .001$
BPRS total score (mean ± *SD*)	24.59 ± 1.14	38.71 ± 8.24	$t_{46} = -7.963$; $P < .001$
SANS total score (mean ± *SD*)	0	24.33 ± 14.20	$t_{46} = -7.126$; $P < .001$

Note: ARMS, at-risk mental state; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; HC, healthy control; MWT-B, Mehrfachwahl-Wortschatz-Test Form B; (Multiple Choice Vocabulary Test); SANS, Scale for the Assessment of Negative Symptoms; *SD*, standard deviation.

Furthermore, corrected for the number of rich-club regions, we found significantly reduced local efficiency of the right accumbens (P = .0062) (figure 3C) and a statistical trend for reduced local efficiency of the left putamen (P = .090) in ARMS subjects compared with HCs. There was also a strong statistical trend for reduced clustering of the left amygdala (P = .0532) and significantly reduced clustering of the left accumbens (P = .0059) (figure 3D). Finally, across all participants, there were significant positive correlations between rich-club organization and local efficiency of the right accumbens (r = .328, P = .023) and local clustering of the left accumbens (r = .473, P = .001) and left amygdala (r = .449, P = .001).

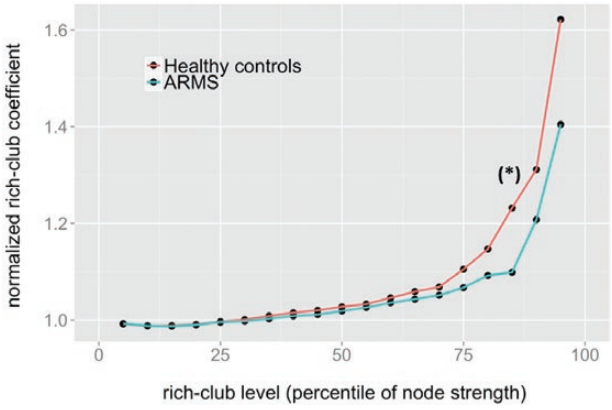

Fig. 1. Normalized rich-club coefficient (Φ^{w}_{norm}) at different rich-club levels expressed as the percentile of node strength for healthy controls (n = 24) and at-risk mental state (ARMS) subjects. (*) significantly reduced Φ^{w}_{norm} in ARMS subjects compared with healthy controls.

Relation Between Rich-Club Organization, Global Functioning, and Symptomatology

In ARMS subjects, there was a significant negative correlation between the area under the rich-club curve and negative psychotic symptoms (SANS total score; r = −.506, P = .012, corrected for multiple correlations) (figure 4A) but not positive psychotic symptoms (r = .023, P = .914) and global functioning (GAF score; r = .222, P = .298).

Across all participants, global functioning correlated positively with the area under the rich-club curve (r = .440, P = .002, corrected for multiple correlations) (figure 4B) and negatively with modularity (r = −.305, P = .035, uncorrected for multiple correlations) (figure 4C).

Discussion

To our knowledge, this is the first graph theoretical DTI study in clinical high-risk subjects for psychosis. The main finding of this study is impaired structural rich-club organization in clinical high-risk subjects for psychosis compared with HCs. This result extends previous findings in schizophrenia patients[9] and unaffected siblings[23] and also resonates with a study in individuals with a chromosome

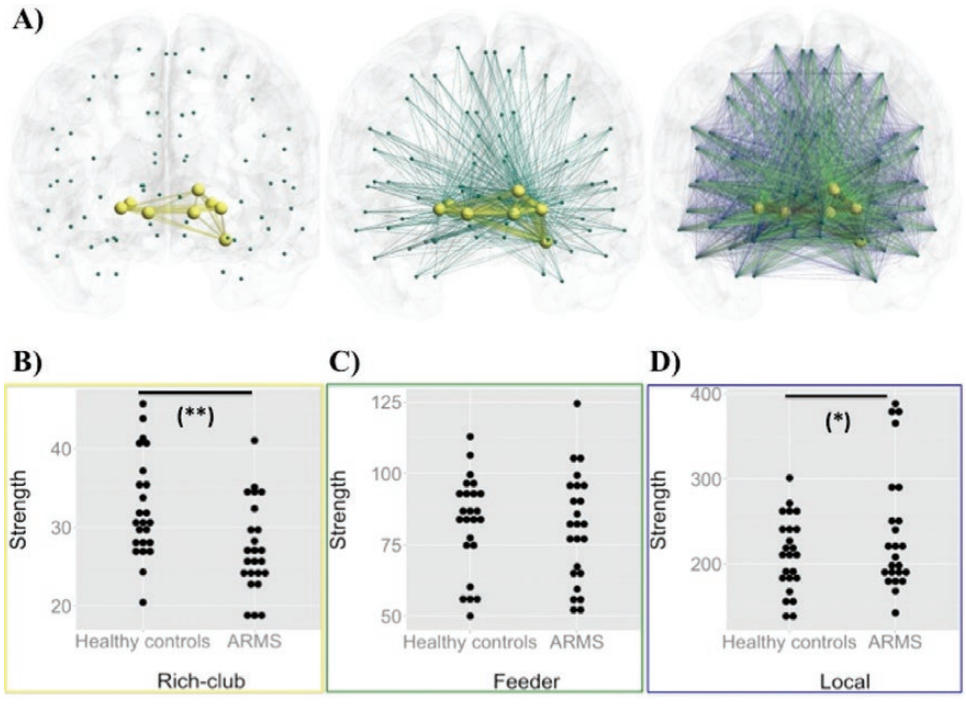

Fig. 2. (A) Structural network organization. Rich-club regions, including the bilateral putamen, pallidum, accumbens, and the left caudate and amygdala and their connections among each other, are depicted in yellow, while feeder connections are depicted in green and local connections in blue. Dotplots represent strength of (B) rich-club, (C) feeder, and D) local connections in at-risk mental state (ARMS) subjects compared and healthy controls. (**) significant group difference at P = .0207, (*) statistical trend for group difference at P = .0549.

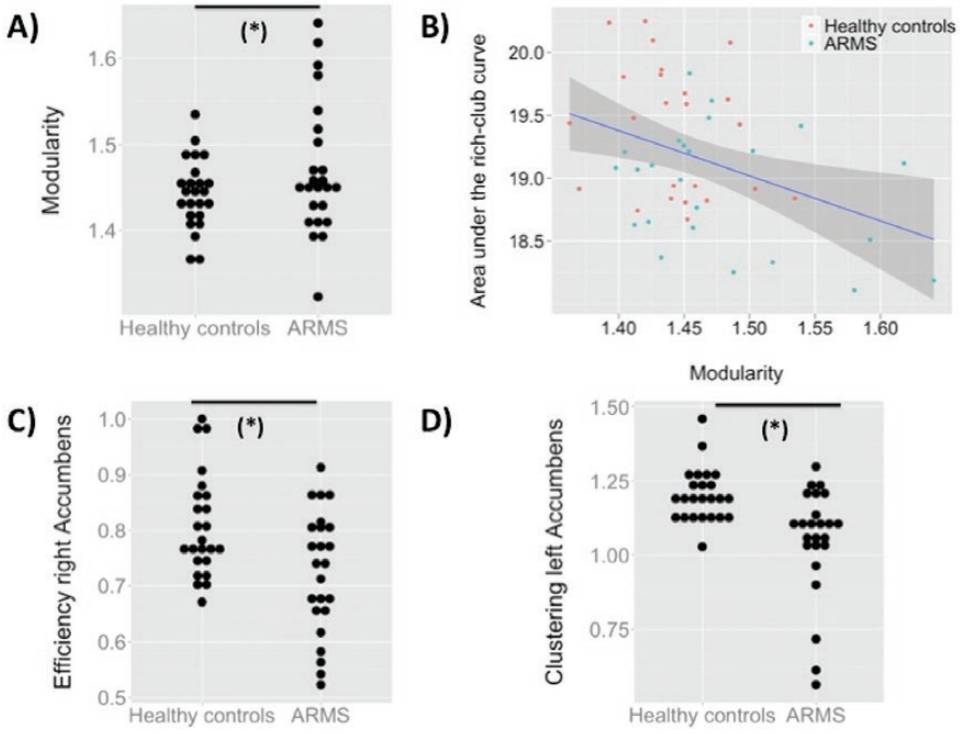

Fig. 3. (A) Modularity values in healthy controls and in at-risk mental state (ARMS) subjects. (B) Negative relation between the area under the rich-club curve and modularity across all participants ($r = -.388$, $P = .007$). (C) Efficiency values of the right accumbens in healthy controls and in ARMS subjects. (D) Clustering values of the left accumbens in healthy controls and in ARMS subjects. (*) significant group differences.

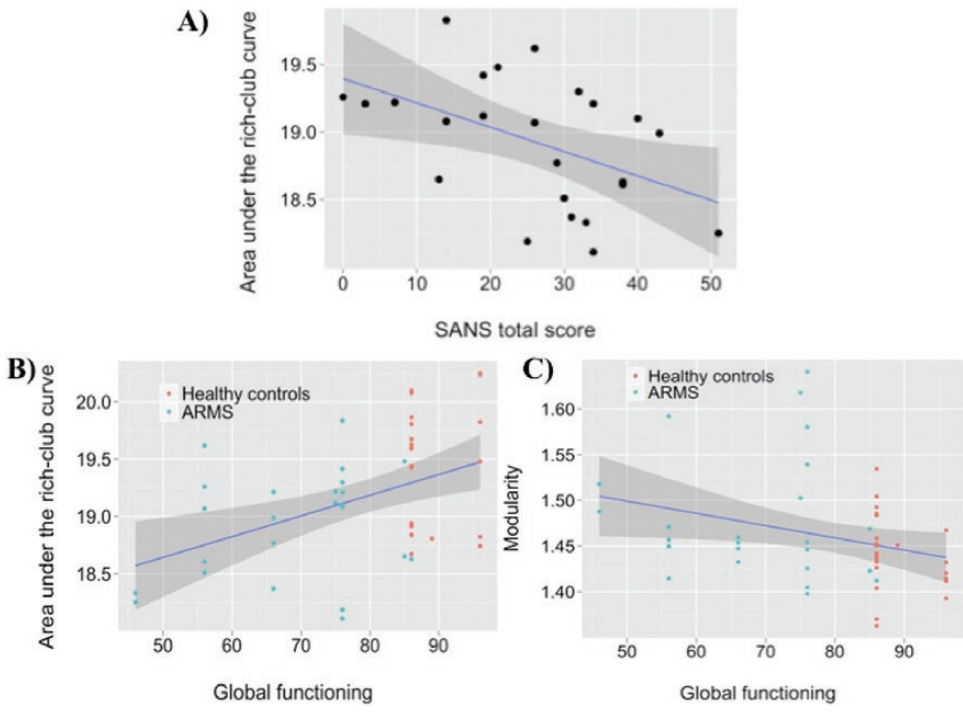

Fig. 4. (A) In at-risk mental state (ARMS) subjects, negative psychotic symptoms were inversely related to the area under the rich-club curve ($r = -.506$, $P = .012$). Across all participants, global functioning were (B) positively related to the area under the rich-club curve ($r = .440$, $P = .002$) and (C) negatively related to modularity ($r = -.305$, $P = .035$).

22q11.2 deletion syndrome reporting reduced connectivity strength among A-core regions, which exhibited stronger-than-expected interconnectivity and thus resemble a weighted rich-club.[16] These findings together support the notion that a breakdown of hub network connectivity may constitute a core pathoconnectomical hallmark of psychosis[6,7,22] and already exists in clinical high-risk samples, suggesting the potential of network connectivity measures to predict outcomes in psychosis.[43–46]

The second major finding was that the level of rich-club disorganization in ARMS subjects correlated with the severity of negative symptoms, which may also have some translational impact, given that negative symptoms are refractory to all available treatments.[47] The identified rich-club regions in this study comprised the dorsal and ventral striatum, the globus pallidus, and the amygdala. Consistent with a previous meta-analysis[48] and multicentre study in subjects at clinical high risk for psychosis,[49] we found no volumetric group differences in these regions, indicating that the group difference in rich-club organization was not due to microstructural changes in these regions. Across the rich-club regions, we found that ARMS subjects revealed significantly reduced local efficiency of the right accumbens and a trend for reduced efficiency of the left putamen, while they also showed significantly reduced clustering of the left accumbens and a strong statistical trend for reduced clustering of the left amygdala. Notably, rich-club organization was positively related to local efficiency of the right accumbens and local clustering of the left accumbens and left amygdala across all participants, suggesting that the reduced strength of rich-club connections in ARMS subjects is probably associated with reduced local efficiency and clustering of the bilateral accumbens and the left amygdala. It has long been proposed that altered dopaminergic projections within the limbic-striatal circuitry affect emotional and motivational behavior in schizophrenia.[50,51] Striatal dopamine function is abnormally elevated both in schizophrenia and in high-risk subjects[52–54] and the aberrant salience hypothesis proposes that this causes attribution of salience to contextually irrelevant stimuli but also to reduced attribution of salience to relevant cue features such as reward-indicating cues.[55,56] A recent meta-analysis showed that reduced ventral striatal activation in response to reward-predicting cues correlated with the severity of negative symptoms in schizophrenia spectrum disorders.[57] Our finding of reduced structural limbic-striatal connectivity may thus reflect a scaffold for impaired reward-related salience processing in psychosis, which might contribute to the formation of negative symptoms. However, a lack of a significant relationship between abnormal structural rich-club connectivity and positive psychotic symptoms does not necessarily mean that no such relation exists. More studies with more accurate assessments of positive symptoms (eg, The Scale for the Assessment of Positive Symptoms) are needed to draw robust inferences on the relationship between abnormal structural rich-club organization and the formation of psychotic symptoms.

The limbic-striatal regions identified as rich-club members in the present study overlap with rich-club regions from recent DTI studies,[16,58] but they also differ from other established rich-club regions, which included the bilateral thalamus, precuneus, superior frontal and superior parietal cortex, insula, and hippocampus.[9,20,59] Different reasons may explain this discrepancy across studies and among others we like to mention a few potential explanations: First, network models have previously shown that rich-club members and their connections may substantially change with respect to the richness factor.[40] Second, different normalization strategies have been performed to adjust the streamline numbers for the size of the nodes/regions. While other studies normalized the streamlines connecting 2 regions of interest by the sum of their volumes,[9,20,59] the cortical surface area,[16] or streamline length,[58] we normalized the streamline number by the product of the voxel numbers of node *i* and *j*. Third, there is no clear identified measure of what is a good index of structural strength.[60] In our study, the weight is based on the reliability with which the tracts were reconstructed, which is different from the number of streamlines reconstructed (volume) used in previous studies.[9,20]

Consistent with a finding in chronic patients,[9] we found an elevated level of modularity in high-risk subjects compared with HCs, reflecting a more segregated pattern of network organization. Notably, the increase in modularity was mediated by the disruption of rich-club organization in high-risk subjects, supporting the pivotal role of the rich-club in the integration of information between segregated brain modules.[21] Furthermore, albeit only at a statistical trend level, the strength of local connections was increased in ARMS subjects relative to HCs. These findings suggest that neural dysmodularity in clinical high-risk subjects is caused by a reduction in rich-club connectivity, which in turn may drive hyperconnectivity in peripheral regions.

Several issues merit comments. We used a probabilistic tractography method to map whole-brain white matter connectivity, which has advantages in tracking specific white matter tracts relating to fiber crossing compared with deterministic tractography methods.[36] However, such a probability-based approach could introduce spurious white matter connections that are biologically not connected. Consistent with other structural rich-club analyses,[9,20,23,61] we decided not to threshold our individual connectivity matrices because (*a*) every (or range of) statistical threshold is arbitrary and not informed by biological evidence and (*b*) small (and presumably false) edge weights will have inconsequential effects on the computed metrics.[8] However, new permutation-based methods may overcome the threshold issue in graph theoretical whole-brain analysis and are thus of interest for future network

studies.[62] The small number of ARMS subject who developed psychosis limits the sensitivity of our exploratory analyses addressing psychosis transition. Ongoing multisite projects in high-risk subjects may be best suited to test the generalizability of our findings. Finally, some of the ARMS subjects received low doses of antidepressants, which may have influenced our findings. In this study, the numbers of untreated and antidepressant-treated subjects were too small to allow for meaningful subgroup analyses and this issue would be better addressed in longitudinal studies that were explicitly linked to study the effect of antidepressants on rich-club connectivity.

In summary, this study extends previous evidence in chronic patients[9] and unaffected siblings of schizophrenia patients[23] by showing impaired structural rich-club organization in clinical high-risk subjects for psychosis. It further highlights the role of structural rich-club connectivity as the backbone for network-wide information integration[21] and shows a breakdown of this interplay in clinical high-risk subjects for psychosis.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. van den Heuvel MP, Fornito A. Brain networks in schizophrenia. *Neuropsychol Rev*. 2014;24:32–48.
2. Fornito A, Zalesky A, Pantelis C, Bullmore ET. Schizophrenia, neuroimaging and connectomics. *Neuroimage*. 2012;62:2296–2314.
3. Rubinov M, Bullmore E. Schizophrenia and abnormal brain network hubs. *Dialogues Clin Neurosci*. 2013;15:339–349.
4. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 2009;10:186–198.
5. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. *Nat Rev Neurosci*. 2015;16:159–172.
6. Rubinov M, Bullmore E. Fledgling pathoconnectomics of psychiatric disorders. *Trends Cogn Sci*. 2013;17:641–647.
7. Crossley NA, Mechelli A, Scott J, et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain*. 2014;137:2382–2395.
8. van den Heuvel MP, Mandl RC, Stam CJ, Kahn RS, Hulshoff Pol HE. Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. *J Neurosci*. 2010;30:15915–15926.
9. van den Heuvel MP, Sporns O, Collin G, et al. Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA Psychiatry*. 2013;70:783–792.
10. Wang Q, Su TP, Zhou Y, et al. Anatomical insights into disrupted small-world networks in schizophrenia. *Neuroimage*. 2012;59:1085–1093.
11. Skudlarski P, Jagannathan K, Anderson K, et al. Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. *Biol Psychiatry*. 2010;68:61–69.
12. Zalesky A, Fornito A, Seal ML, et al. Disrupted axonal fiber connectivity in schizophrenia. *Biol Psychiatry*. 2011;69:80–89.
13. Sun Y, Chen Y, Lee R, Bezerianos A, Collinson SL, Sim K. Disruption of brain anatomical networks in schizophrenia: a longitudinal, diffusion tensor imaging based study. *Schizophr Res*. 2016;171:149–157.
14. Drakesmith M, Caeyenberghs K, Dutt A, et al. Schizophrenia-like topological changes in the structural connectome of individuals with subclinical psychotic experiences. *Hum Brain Mapp*. 2015;36:2629–2643.
15. Ottet MC, Schaer M, Debbané M, Cammoun L, Thiran JP, Eliez S. Graph theory reveals dysconnected hubs in 22q11DS and altered nodal efficiency in patients with hallucinations. *Front Hum Neurosci*. 2013;7:402.
16. Váša F, Griffa A, Scariati E, et al. An affected core drives network integration deficits of the structural connectome in 22q11.2 deletion syndrome. *Neuroimage Clin*. 2016;10:239–249.
17. Li Y, Liu B, Hou B, et al. Less efficient information transfer in Cys-allele carriers of DISC1: a brain network study based on diffusion MRI. *Cereb Cortex*. 2013;23:1715–1723.
18. Shi F, Yap PT, Gao W, Lin W, Gilmore JH, Shen D. Altered structural connectivity in neonates at genetic risk for schizophrenia: a combined study using morphological and white matter networks. *Neuroimage*. 2012;62:1622–1633.
19. van den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci*. 2013;17:683–696.
20. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. *J Neurosci*. 2011;31:15775–15786.
21. van den Heuvel MP, Sporns O. An anatomical substrate for integration among functional networks in human cortex. *J Neurosci*. 2013;33:14489–14500.
22. Crossley NA, Mechelli A, Ginestet C, Rubinov M, Bullmore ET, McGuire P. Altered hub functioning and compensatory activations in the connectome: a meta-analysis of functional neuroimaging studies in schizophrenia. *Schizophr Bull*. 2016;42:434–442.
23. Collin G, Kahn RS, de Reus MA, Cahn W, van den Heuvel MP. Impaired rich club connectivity in unaffected siblings of schizophrenia patients. *Schizophr Bull*. 2014;40:438–448.
24. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70:107–120.
25. Johnstone EC, Lawrie SM, Cosway R. What does the Edinburgh high-risk study tell us about schizophrenia? *Am J Med Genet*. 2002;114:906–912.
26. Smieskova R, Marmy J, Schmidt A, et al. Do subjects at clinical high risk for psychosis differ from those with a genetic high risk?–A systematic review of structural and functional brain abnormalities. *Curr Med Chem*. 2013;20:467–481.

27. Fusar-Poli P, Bechdolf A, Taylor MJ, et al. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophr Bull*. 2013;39:923–932.
28. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*. 2012;69:220–229.
29. Riecher-Rössler A, Aston J, Ventura J, et al. [The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity]. *Fortschr Neurol Psychiatr*. 2008;76:207–216.
30. Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. *Schizophr Bull*. 1986;12:578–602.
31. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry Suppl*. 1989;7:49–58.
32. Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand*. 1995;91:335–345.
33. Yung AR, Phillips LJ, McGorry PD, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl*. 1998;172:14–20.
34. Fischl B. FreeSurfer. *Neuroimage*. 2012;62:774–781.
35. Behrens TE, Woolrich MW, Jenkinson M, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med*. 2003;50:1077–1088.
36. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage*. 2007;34:144–155.
37. Cao Q, Shu N, An L, et al. Probabilistic diffusion tractography and graph theory analysis reveal abnormal white matter structural connectivity networks in drug-naive boys with attention deficit/hyperactivity disorder. *J Neurosci*. 2013;33:10676–10687.
38. Gong G, Rosa-Neto P, Carbonell F, Chen ZJ, He Y, Evans AC. Age- and gender-related differences in the cortical anatomical network. *J Neurosci*. 2009;29:15684–15693.
39. Colizza C, Flammini A, Serrano M, Vespignani A. Detecting rich-club ordering in complex networks. *Nat Phys* 2006;2:110–115.
40. Opsahl T, Colizza V, Panzarasa P, Ramasco JJ. Prominence and control: the weighted rich-club effect. *Phys Rev Lett*. 2008;101:168702.
41. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*. 2010;52:1059–1069.
42. Newman ME. Modularity and community structure in networks. *Proc Natl Acad Sci U S A*. 2006;103:8577–8582.
43. Schmidt A, Diwadkar VA, Smieskova R, et al. Approaching a network connectivity-driven classification of the psychosis continuum: a selective review and suggestions for future research. *Front Hum Neurosci*. 2014;8:1047.
44. McGuire P, Sato JR, Mechelli A, Jackowski A, Bressan RA, Zugman A. Can neuroimaging be used to predict the onset of psychosis? *Lancet Psychiatry*. 2015;2:1117–1122.
45. Schmidt A, Smieskova R, Aston J, et al. Brain connectivity abnormalities predating the onset of psychosis: correlation with the effect of medication. *JAMA Psychiatry*. 2013;70:903–912.
46. Schmidt A, Palaniyappan L, Smieskova R, et al. Dysfunctional insular connectivity during reward prediction in patients with first-episode psychosis. *J Psychiatry Neurosci*. 2016;41:150234.
47. Fusar-Poli P, Papanastasiou E, Stahl D, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull*. 2015;41:892–899.
48. Fusar-Poli P, Radua J, McGuire P, Borgwardt S. Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. *Schizophr Bull*. 2012;38:1297–1307.
49. Mechelli A, Riecher-Rössler A, Meisenzahl EM, et al. Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. *Arch Gen Psychiatry*. 2011;68:489–495.
50. Haber SN, Fudge JL. The interface between dopamine neurons and the amygdala: implications for schizophrenia. *Schizophr Bull*. 1997;23:471–482.
51. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience*. 1991;41:1–24.
52. Egerton A, Chaddock CA, Winton-Brown TT, et al. Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol Psychiatry*. 2013;74:106–112.
53. Howes OD, Bose SK, Turkheimer F, et al. Dopamine synthesis capacity before onset of psychosis: a prospective [18F]-DOPA PET imaging study. *Am J Psychiatry*. 2011;168:1311–1317.
54. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. *Schizophr Bull*. 2013;39:33–42.
55. Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD. Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci*. 2014;37:85–94.
56. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr Bull*. 2010;36:472–485.
57. Radua J, Schmidt A, Borgwardt S, et al. Ventral striatal activation during reward processing in psychosis: a neurofunctional meta-analysis. *JAMA Psychiatry*. 2015;72:1243–1251.
58. Griffa A, Baumann PS, Ferrari C, et al. Characterizing the connectome in schizophrenia with diffusion spectrum imaging. *Hum Brain Mapp*. 2015;36:354–366.
59. McColgan P, Seunarine KK, Razi A, et al.; Track-HD Investigators. Selective vulnerability of rich club brain regions is an organizational principle of structural connectivity loss in Huntington's disease. *Brain*. 2015;138:3327–3344.
60. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage*. 2013;73:239–254.
61. Collin G, de Nijs J, Hulshoff Pol HE, Cahn W, van den Heuvel MP. Connectome organization is related to longitudinal changes in general functioning, symptoms and IQ in chronic schizophrenia. *Schizophr Res*. 2016;173:166–173.
62. Drakesmith M, Caeyenberghs K, Dutt A, Lewis G, David AS, Jones DK. Overcoming the effects of false positives and threshold bias in graph theoretical analyses of neuroimaging data. *Neuroimage*. 2015;118:313–333.