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Archival Report

Affected Anatomical Rich Club and Structural–Functional Coupling in Young Offspring of Schizophrenia and Bipolar Disorder Patients

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ABSTRACT

BACKGROUND: Emerging evidence suggests disruptions in the wiring organization of the brain's network in schizophrenia (SZ) and bipolar disorder (BD). As the importance of genetic predisposition has been firmly established in these illnesses, children (offspring) of patients constitute an at-risk population. This study examines connectome organization in children at familial high risk for psychosis.

METHODS: Diffusion-weighted magnetic resonance imaging scans were collected from 127 nonpsychotic offspring 8 to 18 years of age (average age = 13.5 years) of a parent diagnosed with SZ (SZ offspring; n = 28) or BD (BD offspring; N = 60) and community control subjects (n = 39). Resting-state functional magnetic resonance imaging scans were available for 82 subjects. Anatomical and functional brain networks were reconstructed and examined using graph theoretical analysis.

RESULTS: SZ offspring were found to show connectivity deficits of the brain's central rich club (RC) system relative to both control subjects and BD offspring. The disruption in anatomical RC connectivity in SZ offspring was associated with increased modularity of the functional connectome. In addition, increased coupling between structural and functional connectivity of long-distance connections was observed in both SZ offspring and BD offspring.

CONCLUSIONS: This study shows lower levels of anatomical RC connectivity in nonpsychotic young offspring of SZ patients. This finding suggests that the brain's anatomical RC system is affected in at-risk youths, reflecting a connectome signature of familial risk for psychotic illness. Moreover, finding no RC deficits in offspring of BD patients suggest a differential effect of genetic predisposition for SZ versus BD on the developmental formation of the connectome.

Keywords: Bipolar disorder, Connectome, Familial high-risk, Offspring, Rich club, Schizophrenia

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Elucidating the patterns of brain development that lead up to the manifestation of major psychiatric disorders is a pressing issue in current biological psychiatry. A valuable paradigm to explore brain development in relation to psychiatric vulnerability is the study of young individuals at increased risk for schizophrenia (SZ) and bipolar disorder (BD) (1–3). Given that these illnesses are genetically mediated (4,5), offspring of SZ and BD patients constitute an at-risk population. In addition to genetic predisposition, having a parent with mental illness has been associated with an increased burden of environmental stressors in childhood (6,7) that further increase the risk of developing a psychiatric disorder. Identifying neurobiological disturbances in these at-risk offspring may help clarify the developmental origins of brain abnormalities observed in established illness and contribute to the development of early detection and intervention strategies aimed to ameliorate or prevent psychotic illness (8).

SZ and BD are characterized by symptoms in a range of behavioral, cognitive, and affective domains. These higher-order brain functions depend on flexible interactions among functionally specialized neural circuits, shaped by the brain's network of anatomical connections, the connectome (9). Graph theoretical studies suggest that the connectome is organized according to a cost-efficient wiring pattern (10), with a modular community structure (11), short communication relays (12,13) and a central "rich club" (RC) core of highly connected hubs (14) that is thought to have a crucial role in whole-brain integration (15,16). Emerging evidence suggests that the brain's wiring organization is disrupted in SZ [for review see (17,18)] and BD (19–21), but whether connectome abnormalities are present in unaffected young offspring of SZ and BD patients remains to be determined.

In this study, we examine connectome organization in young offspring of SZ and BD patients. These high-risk offspring between 8 and 18 years of age are younger than the typical age at onset of SZ and BD, which peaks in late teens to early twenties (22–24). Studying this at-risk population

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thus provides an opportunity to assess the impact of genetic vulnerability for psychotic illness on brain development well before the age at which psychosis typically manifests. Investigating anatomical and functional brain network topology, we aim to determine whether disruptions in connectome organization are present in nonpsychotic young at-risk offspring and how putative deficits in connectome topology relate to early psychopathology.

METHODS AND MATERIALS

Participants

This study includes 127 participants between 8 and 18 years of age from a total of 93 families, including 28 offspring of a SZ patient (SZ offspring), 60 offspring of a BD patient (BD offspring), and 39 community control subjects (Table 1). The offspring are referred to as nonpsychotic because none met DSM-IV criteria for SZ or a related psychotic disorder at the time of baseline assessment (present and lifetime). For each family, all offspring in the appropriate age range entered our study to prevent a biased selection of participants within the family, as offspring with (subthreshold) symptoms may otherwise be more likely to be signed up for study participation than offspring with no (subthreshold) symptoms. Clinical diagnoses of parents were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (25). Control parents were screened for psychopathology using the mini-Schedules for Clinical Assessment in Neuropsychiatry (26). The medical ethics committee of the University Medical Center Utrecht approved the study, and all participating children and their parents provided written informed consent.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (27) was used to evaluate symptoms and DSM-IV diagnoses of all participants (Supplement). As evidence suggests that intelligence relates to brain changes during development (28–30) and intellectual underperformance is a risk factor for SZ (31), IQ was also assessed. Overall IQ was estimated using four subtests (block design, picture completion, information, and vocabulary) of the Wechsler Intelligence Scale for Children–Third Edition Revised (for participants ≤16 years of age) (32) or the Wechsler Adult Intelligence Scale–Third Edition (for participants >16 years of age) (33). The majority of the offspring (>85%) were naïve to psychotropic medication.

Table 1. Demographic and Clinical Characteristics

	Schizophrenia Offspring, n = 28	Bipolar Disorder Offspring, n = 60	Community Controls, n = 39	Statistics
Age, Mean (SD)	13.1 (3.1)	14.2 (2.5)[a]	12.7 (2.2)[a]	$F = 3.92$, $p = .022$
Gender, Male/Female, n	9/19	33/27	19/20	$\chi^2 = 4.13$, $p = .127$
Estimated IQ,[b] Mean (SD)	100.4 (20.5)[c]	104.0 (19.1)[a]	116.9 (12.7)[a,c]	$F = 8.69$, $p < .001$
Clinical Diagnosis,[d] n (%)				
No diagnosis	11 (39.3)[c]	28 (46.7)[a]	32 (82.1)[a,c]	$\chi^2 = 15.03$, $p = .001$
Mood disorder[e]	6 (21.4)	18 (30.0)[a]	4 (10.3)[a]	$\chi^2 = 6.05$, $p = .049$
Anxiety disorder[f]	3 (10.7)	4 (6.7)	1 (2.6)	$\chi^2 = 1.85$, $p = .397$
ADHD	1 (3.6)	1 (1.7)	0 (0.0)	$\chi^2 = 1.32$, $p = .516$
ASD	4 (14.3)[c]	2 (3.3)	0 (0.0)[c]	$\chi^2 = 7.63$, $p = .022$
Other[g]	3 (10.7)	4 (6.7)	2 (5.1)	$\chi^2 = 0.77$, $p = .682$
K-SADS Sum Scores,[h] Mean (SD)				
Total	138.6 (14.0)[c]	136.8 (19.2)[a]	122.7 (7.2)[a,c]	$\chi^2 = 12.06$, $p < .001$
Psychosis	34.6 (3.8)[c]	33.5 (3.4)	32.3 (0.6)[c]	$\chi^2 = 4.82$, $p = .010$
Depression	10.6 (2.8)[c]	10.5 (2.8)[a]	8.9 (1.3)[a,c]	$\chi^2 = 5.95$, $p = .003$
Mania	4.6 (1.1)	4.7 (1.7)[a]	4.0 (0.0)[a]	$\chi^2 = 3.65$, $p = .029$
Anxiety	17.0 (3.2)	17.0 (3.5)	15.5 (2.2)	$\chi^2 = 2.83$, $p = .063$
Behavior	20.4 (4.6)[c]	20.3 (4.2)[a]	17.5 (2.0)[a,c]	$\chi^2 = 7.50$, $p = .001$
Psychotropic Medication,[i] n (%)	3 (10.7)	3 (5.0)	0 (0)	$\chi^2 = 3.95$, $p = .139$

Statistical comparison was performed using analysis of variance for continuous and chi-squared tests for categorical variables.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder (including Asperger syndrome and childhood disintegrative disorder); K-SADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children.

[a]Significant bivariate difference (post hoc test): bipolar disorder offspring vs. controls.

[b]Data missing for 4 subjects.

[c]Significant bivariate difference (post hoc test): schizophrenia offspring vs. controls.

[d]Data missing for 3 subjects.

[e]Mood disorders include major depressive disorder, bipolar disorder, dysthymic disorder, cyclothymic disorder, mood disorder not otherwise specified, and adjustment disorder with depressed mood.

[f]Anxiety disorders include panic disorder, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, and anxiety disorder not otherwise specified.

[g]Other includes tic disorder not otherwise specified, eating disorder not otherwise specified, enuresis, adjustment disorder with mixed disturbances of emotions and conduct, oppositional defiant disorder, and cannabis use disorder.

[h]Data missing for 9 subjects.

[i]Psychotropic medications include methylphenidate, dexamphetamine, fluoxetine, citalopram, haloperidol, and melatonin. Data missing for 10 subjects.