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Anatomical Distance Affects Functional Connectivity in Patients With Schizophrenia and Their Siblings

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Background: **The efficiency of human brain depends on the integrity of both long- and short-range connections, but the long-range connections need to be "penalized" to reduce overall wiring costs. This principle, termed as the anatomical distance function (ADF), refers to the presence of an inverse relationship between anatomical distance and connectivity. A crucial developmental feature that occurs in normal adolescence is the weakening of ADF, which is characterized by a selective strengthening of long-distance connections. Schizophrenia is associated with widespread dysconnectivity that is linked to aberrant cortical development.** ***Methods:*** **We studied the ADF in adults with schizophrenia (n = 28), their age-matched siblings (n = 28), and healthy controls (n = 60). We investigated the proportional abnormalities in the long-range connections involving interhemispheric, subcortical, frontal, and salience network regions and localized the connections showing most significant changes in schizophrenia. The groups were discriminated on the basis of short- and long-range connectivity using a machine-learning algorithm.** ***Results:*** **Both patients and their siblings showed abnormally pronounced ADF. This was associated with a disproportionate reduction in the number of long-range connections, affecting the subcortical, interhemispheric, and the salience network connections. The abnormalities in long-range connections had superior ability to accurately identify group membership.** ***Conclusions:*** **A crucial organizing principle of the brain architecture that becomes apparent during normal adolescence is disturbed in schizophrenia. While siblings show some evidence of compensating for this deficit, patients lack putative compensatory changes. Age-related shift in ADF provides an explanatory framework for the developmental emergence of widespread dysconnectivity that is influenced by genetic risk in schizophrenia.**

Key words: anatomical distance/schizophrenia/genetic risk/functional connectivity/wiring cost/salience network

Introduction

Schizophrenia is a highly heritable disorder characterized by several features suggestive of an aberrant brain developmental trajectory.[1–4] The last 2 decades of neuroscientific research has strongly supported the role of dysconnectivity in the pathophysiology of psychotic disorders such as schizophrenia. Dysconnectivity has been demonstrated both at microscale (at neuronal circuit or synaptic level)[5,6] and at mesoscale (using neuroimaging measures of structural and functional connectivity) levels. A wide range of neuroimaging studies, including those investigating grey matter surface,[7] anatomical covariance,[8] white matter diffusion,[9] macromolecular integrity,[10,11] functional correlation,[12,13] and temporal precedence,[14,15] have been interpreted as evidence for dysconnectivity in schizophrenia. These studies have indicated that this dysconnectivity is distributed in nature, affecting the entire brain, though some regions may be affected more than the others. Bulk of evidence points towards consistent involvement of subcortical and frontal systems[16] along with paralimbic salience-processing networks involving the insula, anterior cingulate cortex, and the putamen.[17] Further, interhemispheric connections form a major portion of the functional connectivity in the resting brain[18]; aberrant interhemispheric connectivity has also been prominently observed in schizophrenia.[19,20] Despite

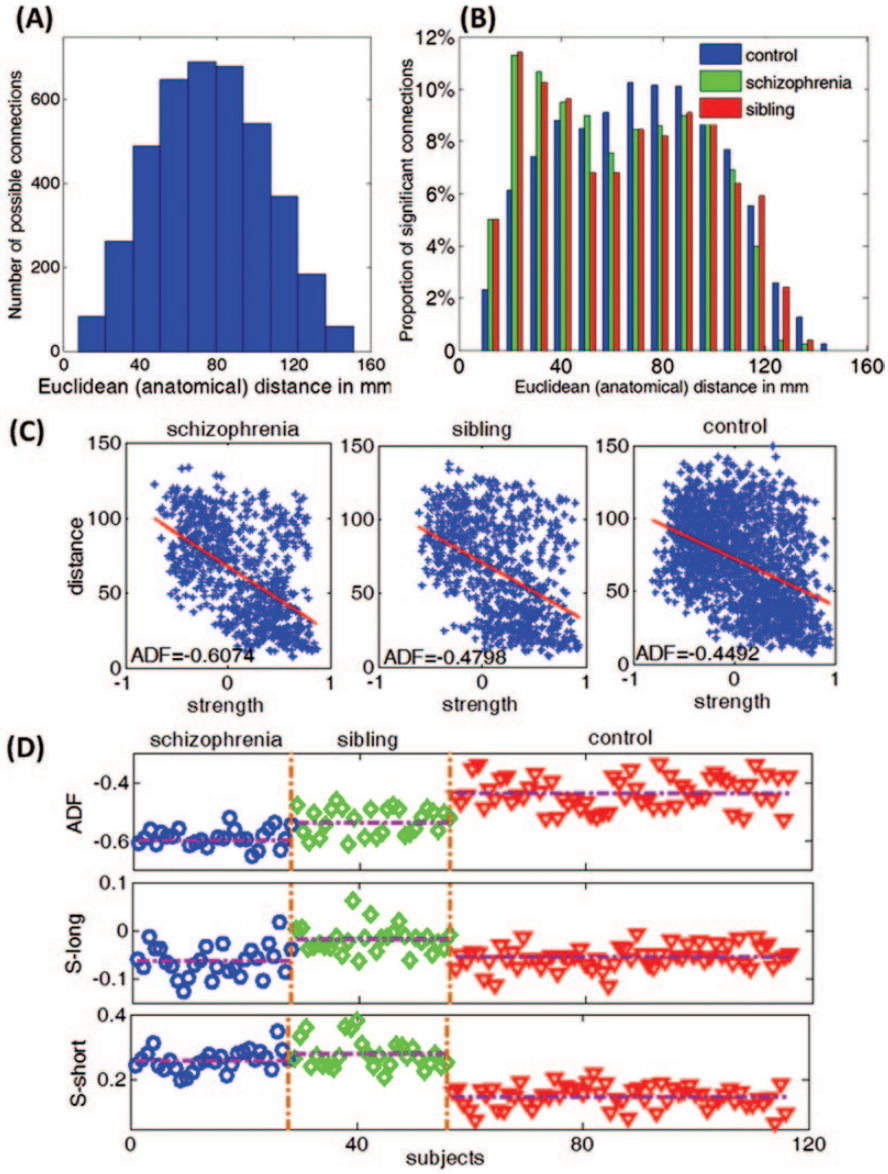

Fig. 1. We wish to print this figure with color reproduction. (A) Histogram of the anatomical distance of all possible connections. The range of the anatomical distance is 7.6~151 mm. We select 75.5 mm as the threshold to divide all possible connections to long-range connections (>75.5 mm, 2004 connections in total) and short-range connections (<75.5 mm, 2001 connections in total). (B) Histogram of the anatomical distance of all functional significant links within each group. **(C)** Anatomical distance function (ADF) of a single subject within each group. There are 779 significant links within group 1(schizophrenia), 780 significant links within group 2 (sibling) and 1186 links within group 3 (control). Blue stars represent these significant links; the slope of the red line is ADF of a single subject. (D) ADF, S-long and S-short for all subjects within each group. The detailed results are shown in table 2.

in patients compared with controls. S-long was significantly reduced (more pronounced negative correlations) in patients but increased (less pronounced negative correlations) in siblings. S-short was significantly increased (more pronounced positive correlations) in both patients and siblings, with siblings showing greater connectivity strength than patients, as shown in figure 1D. Both siblings and patients showed a reduction in P-long and an increase in P-short. These results are shown in figure 2 and table 2. The result of the SVM analysis is presented in the supplementary material.

Frontal, Insular, and Subcortical Systems

ROIs related to frontal network, subcortical network, and salience network are elaborated in supplementary materials. Proportional contribution of frontal regions to the significant short and long-range connections was unaffected in siblings and patients. There was a disproportionate decrease in long-range connections and increase in short-range connections involving subcortical regions in both patients and siblings. An increase in long-range connections involving the salience network was seen in patients. In line with the overall changes in S-long, the

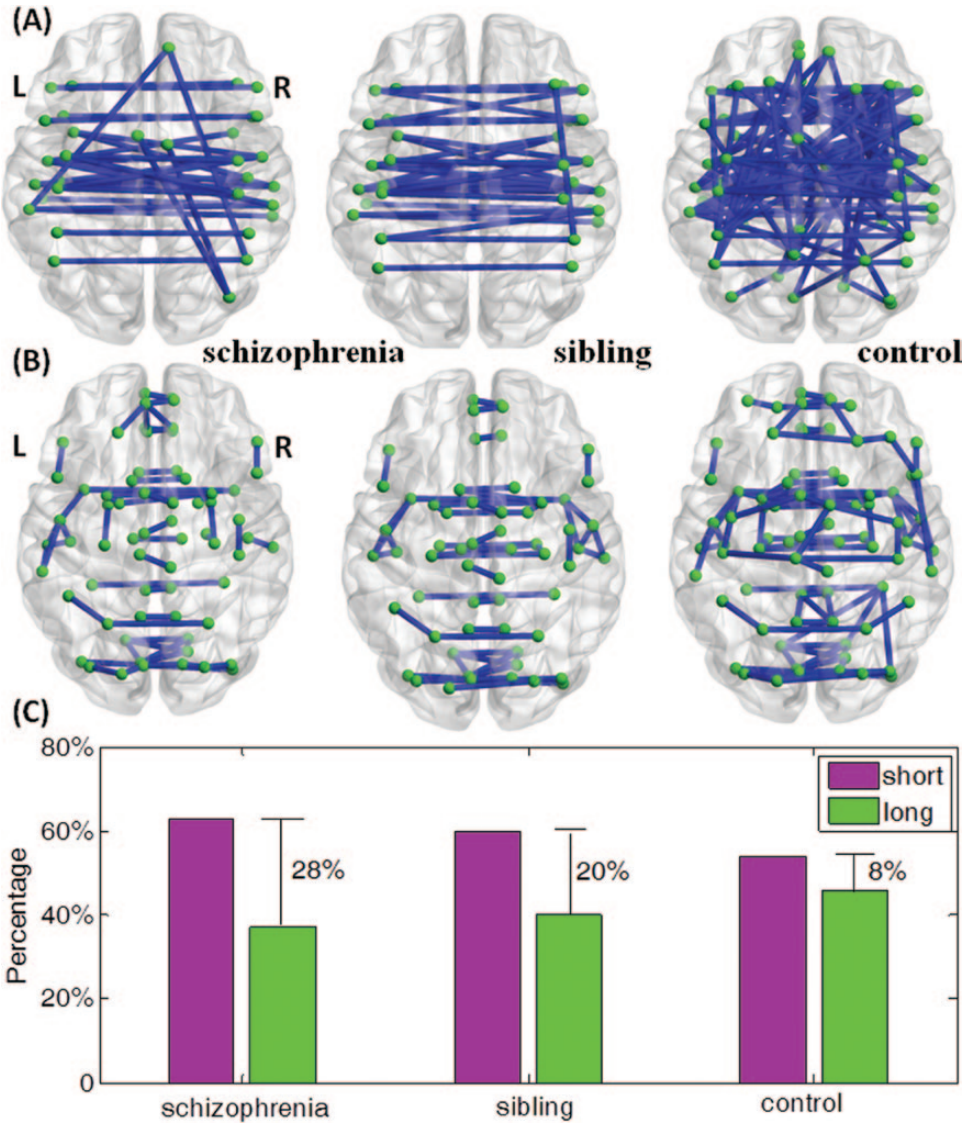

Fig. 2. We wish to print this figure with color reproduction too. The top 10% of significant long links from 1-sample *t* tests within each group are displayed in panel (A). There are 29 long links within schizophrenia group, 31 long links within sibling group, and 76 long links within controls. The top 10% of significant short links within each group are displayed in panel (B). There are 49 short links within schizophrenia group, 47 short links within sibling group and 92 short links within controls. (C) Bar plot of the proportional difference of short links and long links within each group displaying the difference between P-short and P-long shown in table 2.

frontal, insular, and subcortical long-range connections showed more pronounced negative correlations in patients while the short-range connections showed more pronounced positive correlations. Siblings showed either less pronounced negative correlation (frontal, subcortical) or an unexpected positive correlation (salience network) for long links. These results are shown in table 3.

Interhemispheric Links

The proportion of interhemispheric links among all connections was comparable among the groups (49% in controls; 48% in patients, and 51% in siblings). But when the proportion of long-range connections among all interhemispheric connections were considered, 62% of all interhemispheric connections were long range for controls; only 52% were long range in schizophrenia, with 58% being long range in siblings. The mean connectivity strength for interhemispheric links (both short and long-range) was significantly increased (more pronounced positive correlation) in siblings (mean [SD] = 0.141 [0.033]) and patients (mean [SD] = 0.125 [0.037]) when compared with controls (mean [SD] = 0.044 [0.021]) (ANOVA, $F = 141.56$, $P \leq .001$; patients vs controls, $t = 12.93$, $P < .001$; siblings vs controls, $t = 16.64$, $P < .001$; patients vs siblings, $t = -1.74$, $P = .093$).

Localizing Altered Connectivity

Figure S4 (Supplementary Material) is the Manhattan plot of *P* value for all of the possible links, where y-axis

Table 3. Regional Changes of Frontal, Subcortical, and Salience Networks

	Scz	Sib	Con	*t* and χ^2 tests
Frontal network				
Proportion of frontal links among all long links	61%	60%	60%	Scz vs Con: $\chi^2 = 0.0156$, $P = .9007$ Sib vs Con: $\chi^2 = 0.0120$, $P = .8993$ Scz vs Sib: $\chi^2 = 0.0438$, $P = .8342$
S-long	−0.1450 (0.0460)	−0.0684 (0.0308)	−0.0805 (0.0297)	ANOVA, $F = 42.61$, $P < .001$ Scz vs Con: $t = -7.8828$, $P < .001$ Sib vs Con: $t = 1.7609$, $P = .0818$ Scz vs Sib: $t = -6.4795$, $P < .001$
S-short	0.2022 (0.0369)	0.2538 (0.0428)	0.1140 (0.0343)	ANOVA, $F = 150.2$, $P < .001$ Scz vs Con: $t = 10.9656$, $P < .001$ Sib vs Con: $t = 16.4385$, $P < .001$ Scz vs Sib: $t = 4.6471$, $P < .001$
Subcortical network				
Proportion of subcortical links among all long links	7%	7%	13%	Scz vs Con: $\chi^2 = 8.4627$, $P = .0036$ Sib vs Con: $\chi^2 = 7.7226$, $P = .0055$ Scz vs Sib: $\chi^2 = 0.0477$, $P = .8270$
S-long	−0.2051 (0.0558)	−0.1322 (0.0510)	−0.1135 (0.0514)	ANOVA, $F = 29.87$, $P < .001$ Scz vs Con: $t = -7.5688$, $P < .001$ Sib vs Con: $t = -1.5875$, $P = .1161$ Scz vs Sib: $t = -7.9391$, $P < .001$
S-short	0.2679 (0.0569)	0.3107 (0.0894)	0.1738 (0.0602)	ANOVA, $F = 45$, $P < .001$ Scz vs Con: $t = 6.9424$, $P < .001$ Sib vs Con: $t = 8.4614$, $P < .001$ Scz vs Sib: $t = -2.1696$, $P = .0390$
SN				
Proportion of SN links among all long links	16%	15%	12%	Scz vs Con: $\chi^2 = 4.0964$, $P = .0430$ Sib vs Con: $\chi^2 = 1.9501$, $P = .1626$ Scz vs Sib: $\chi^2 = 0.2873$, $P = .5919$
S-long	−0.0670 (0.0426)	0.0265 (0.0602)	−0.0169 (0.0439)	ANOVA, $F = 27.07$, $P < .001$ Scz vs Con: $t = -5.0434$, $P < .001$ Sib vs Con: $t = 3.8472$, $P < .001$ Scz vs Sib: $t = -6.6405$, $P < .001$
S-short	0.2392 (0.0387)	0.3265 (0.0813)	0.2135 (0.0590)	ANOVA, $F = 32.8$, $P < .001$ Scz vs Con: $t = 2.1036$, $P = .0383$ Sib vs Con: $t = 7.3948$, $P < .001$ Scz vs Sib: $t = -5.2443$, $P < .001$

Note: SN, salience network; abbreviations are explained in the footnote to table 2.

must be recruited in service of the task, resulting in inefficient but excessive recruitment. Several fMRI studies of task performance in patients support this notion.[47–49]

We observed that in siblings, though the ADF is perturbed, there is some degree of recovery or compensation. Though long links are reduced in proportion, there is a degree of strengthening of relationship among the existing links, which is not seen in patients. This observation is strikingly reminiscent of the structural studies that demonstrate "normalization" of deficits along the developmental trajectory in siblings.[1] While higher genetic loading in patients could be invoked to explain the lack of such "recovery," another possibility is the effect of environmental agents such as cannabis and stimulants. Exposure to cannabis at developmentally critical time windows appears to have a selective effect on the integrity of structural connections.[50] Direct intracortical animal studies suggest that ketamine, which has a propensity to trigger psychotic symptoms, induces decoupling of long-range connections—a finding analogous to the observations made in the present study in patients with schizophrenia.[51]

Alexander-Bloch et al.[34] investigated the relationship between anatomical distance and functional connectivity strength using a graph-based approach in childhood-onset schizophrenia (mean [SD] age at scan = 18.7 [4.9]; mean [SD] age of onset = 10 [1.8]). In line with our results, stronger connections were noted at shorter anatomical distances in both controls and patients. Further, the mean connection distance in sparsely thresholded networks from healthy participants (44 mm) was strikingly similar to the value obtained in our study (45 mm). Despite these similarities, COS group had relatively normal functional connectivity when long-distance links were considered. The greatest disturbance in connectivity in COS was noted for short-distance connections. In contrast to the approach used in our study, Alexander-Bloch et al.

Table 4. The Links With Significant Difference Between the Groups After Bonferroni Correction

(1) Patients With Schizophrenia vs Healthy Controls

	Links	Connectivity strength in Scz	Connectivity strength in Con	*P* value ($\times 10^{-4}$)	Distance (mm)
1	SMG.L−IFGtriang.R	0.0590	0.3132	.0005	124.8877
2	TPOmid.R−FFG.R	0.0129	0.2471	.0096	55.9338
3	PCUN.L−SFGmed.R	−0.0597	0.2539	.0118	109.6049
4	SMG.L−IFGoperc.R	0.1267	0.4011	.0154	116.9594
5	ITG.R−MTG.R	0.4214	0.1612	.0187	22.0671
6	MTG.L−CAL.L	−0.2171	0.0816	.0201	66.5477
7	TPOsup.R−FFG.R	−0.1440	0.0712	.0202	55.8101
8	TPOmid.R−IFGtriang.R	0.0992	−0.1339	.0414	49.3352
9	INS.L−ORBinf.R	0.0286	0.2819	.0480	81.9712
10	TPOsup.L−MOG.R	−0.1717	0.0542	.0569	128.5824
11	SFGdor.R−SPG.L	−0.2539	0.0490	.0580	102.5120
12	SFGdor.R−IPL.L	−0.2361	0.0409	.0708	100.5703
13	SFGdor.R−ORBinf.R	0.1041	−0.1389	.0833	58.9943
14	PUT.R−INS.L	0.2892	0.4757	.1069	62.9417
15	ITG.L−PCUN.R	0.0539	−0.1630	.1103	93.9948

(2) Siblings vs Healthy Controls

	Links	Connectivity strength in Sib	Connectivity strength in Con	*P* value ($\times 10^{-4}$)	Distance (mm)
1	ANG.L−SPG.R	0.0248	−0.2638	.0000	75.0894
2	PCUN.L−SFGmed.R	−0.0475	0.2539	.0417	109.6049
3	AMYG.L−SMA.L	0.0984 0.0984	−0.1282	.1080	80.7345
4	TPOsup.L−MOG.R	−0.1550	0.0542	.1220	128.5824

(3) Patients With Schizophrenia vs Siblings

	Links	Connectivity strength in Scz	Connectivity strength in Sib	*P* value ($\times 10^{-4}$)	Distance (mm)
1	INS.L−REC.R	−0.3176	−0.0286	.0108	56.5006
2	INS.R−REC.R	−0.3175	−0.0157	.0270	47.0025

Note: Scz, patients with schizophrenia; Sib, siblings, Con, controls. The descriptors for regions-of-interest are provided in the Supplementary Material.

considered only absolute values of functional connectivity (ie, negative correlations were treated as positive correlations) and the connectivity matrices were binarized to derive topological metrics from 293 brain regions, in contrast to the 90 used in our study. These methodological differences preclude meaningful comparison of the 2 results. But if a true difference exists in the direction of relationship between anatomical distance and connectivity between COS and adult-onset schizophrenia, then the ADF could be considered as an important biological variable potentially influencing the age of onset of schizophrenia.

The subcortical system showed a disproportionate reduction in the number of long-range connections and an increase in short-range connections in schizophrenia. An increase in short-range connectivity involving subcortical structures in schizophrenia has been well documented previously.[52,53] There is also a selective reduction of interhemispheric long links in schizophrenia, though when short-range connections are also taken into account, the overall strength of connections shifts towards higher positive correlation in patients. These observations reconcile previously reported inconsistent evidence regarding the increase[54,55] or decrease[19,20] in interhemispheric transfer, highlighting the importance of exploring anatomical distance while studying functional connectivity in schizophrenia.

Two long-range interhemispheric connections (left precuneus with right medial superior frontal and left temporal pole to right middle occipital gyrus) showed common abnormality in patients and siblings. Siblings showed an unexpected positive correlation in the long-range connections involving the salience network nodes, while patients showed more pronounced anticorrelation. The localization of altered connectivity changes revealed that indeed the greatest difference between siblings and patients related to the connectivity between insula and a portion of the orbitofrontal cortex (rectus gyrus). These observations are interesting in the context of structural studies, which show that the anatomical changes pertaining to

the insula is only apparent in patients and not siblings.[56] Several lines of evidence now point towards abnormalities in the salience-processing system as a cardinal feature of several core psychotic symptoms.[17] The present results reaffirm this notion and additionally suggest that genetically high-risk siblings, who do not have clinical psychotic illness, may have a selective strengthening of the long-range connections involving the salience network, which confers them with a protective effect. In fact, the establishment of structural and dynamic causal connectivity between insula and rest of the brain appears to be a crucial maturational event during adolescence.[57] Despite sharing the ADF abnormality with patients, siblings show an excessive strengthening of the salience network–related long-range connections. This phenomenon calls for further investigation of the developmental cortical maturation in siblings using a longitudinal design. If a critical difference in the salience network connectivity is indeed the step change between resilience and psychosis in genetically predisposed individuals, then modulating the salience-processing networks may offer therapeutic opportunities in psychosis.

Several limitations must be borne in mind while interpreting this study. We approached the issue of connectivity using arbitrary anatomical parcellations. This approach is not unconventional; the atlas-based parcellation scheme may facilitate replication of the current work with other data sets. Nevertheless, the functional correspondence of AAL regions is unclear at present. In line with a number of other studies, we used a correlation-based approach to infer brain connectivity, but we did not measure other graph metrics. While the study of topological properties of functional networks is a very interesting area,[58,59] our primary interest was the relationship between anatomical distance and the strength of interregional resting-state correlations. Our approach allowed a direct test of our hypothesis, without requiring other topological metrics. Seventy-five percent of our patients were medicated. Antipsychotic medications may attenuate functional connectivity patterns in the short term,[60,61] though to our knowledge, there is no evidence to suggest that the ADF is altered by the use of antipsychotics. The absence of experimental evidence to support or refute the effect of antipsychotics on ADF calls for cautious interpretation of our results. We have addressed this issue further in the supplementary material.

In summary, the relationship between anatomical distance and functional connectivity is significantly altered in schizophrenia. The observed abnormalities suggest that the normal adolescent maturational process goes awry in those with a genetic diathesis to develop psychosis, but siblings who are "resilient" to the clinically expressed illness show a degree of normalization or "protective" changes that are absent in patients. Our findings offer a converging framework to examine the effects of genetic risk factors for psychosis on the developing brain. They also raise the question whether the disturbances in the organizing principles of brain connectivity seen in schizophrenia may confer some degree of genetically determined metabolic cost advantage.

Supplementary Material

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

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