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Aberrant Functional Whole-Brain Network Architecture in Patients With Schizophrenia: A Meta-analysis

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Findings from multiple lines of research provide evidence of aberrant functional brain connectivity in schizophrenia. By using graph-analytical measures, recent studies indicate that patients with schizophrenia exhibit changes in the organizational principles of whole-brain networks and that these changes relate to cognitive symptoms. However, there has not been a systematic investigation of functional brain network changes in schizophrenia to test the consistency of these changes across multiple studies. A comprehensive literature search was conducted to identify all available functional graph-analytical studies in patients with schizophrenia. Effect size measures were derived from each study and entered in a random-effects meta-analytical model. All models were tested for effects of potential moderator variables as well as for the presence of publication bias. The results of a total of n = 13 functional neuroimaging studies indicated that brain networks in patients with schizophrenia exhibit significant decreases in measures of local organization ($g = -0.56$, $P = .02$) and significant decreases in small-worldness ($g = -0.65$, $P = .01$) whereas global short communication paths seemed to be preserved ($g = 0.26$, $P = .32$). There was no evidence for a publication bias or moderator effects. The present meta-analysis demonstrates significant changes in whole brain network architecture associated with schizophrenia across studies.

Key words: schizophrenia/connectivity/cognition/graph analysis/meta-analysis

Introduction

Multiple studies indicate that schizophrenia is associated with changes in specific brain regions[1–4] and functions.[5,6] However, it has long been argued that these localized abnormalities cannot account for the manifold clinical and cognitive symptoms experienced by affected patients. Instead, Wernicke[7] and Kraepelin[8] first suggested that schizophrenia could be best understood as a neuropathology of connections between brain regions. This "dysconnectivity" hypothesis has stimulated a whole field of research,[9–11] and numerous neuroimaging studies report evidence for abnormal brain connectivity in patients with schizophrenia across modalities.[9,12,13]

Functional brain connectivity can be determined by calculating the statistical dependency between neurophysiological signals measured by correlation coefficients or mutual information metrics, as employed in functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) data. Most functional studies of brain connectivity in patients with schizophrenia have focussed on isolated circuits based on hypotheses related to abnormal behavior, such as dopaminergic pathways of fronto-striatal regions,[6,14–16] language subnetworks,[17] or subnetworks of cognitive control.[18] However, a centrally important question is whether the network abnormalities are spatially restricted to such circuits or whether the integrity of brain functioning is globally disrupted.

The recent introduction of quantitative network analysis to the analysis of neuroimaging data[19–21] has facilitated research of global aberrant connectivity patterns in schizophrenia.[22] This approach represents a methodological framework in which brain connectivity patterns are represented as a network of connections ("edges") between brain regions ("nodes"). Nodes have been defined as voxels,[23] regions of interest[24] or brain networks.[25] Most importantly, this representation of brain connectivity allows the characterization of the structure or organizational principles of whole brain networks and thus extends beyond the investigation of individual connections or isolated circuits. Moreover, graph-theoretical measures can be used to quantify the degree to which brain networks follow certain principles of organization and how they differ between individual subjects or different patient populations.

Graph-analytical studies of schizophrenia can be understood with reference to the concepts of "global short communication paths" and "local organization." Networks with highly expressed global short communications paths often show a high degree of integration and thus hold important advantages as they allow information to be transmitted rapidly across different nodes. The degree of integration of brain networks can be quantified by graph-analytical measures like "global efficiency" and "average minimal path length."[26] Another important architecture frequently observed in brain networks is the local organization into functionally independent subsets of regions. Networks with high local organization allow efficient computation on the local level and are resilient to failure of individual nodes. In graph-analysis, this organization can be quantified by measures such as the "clustering coefficient," "transitivity" or "modularity."[26] Most interestingly, it has also been shown that brain networks follow a so-called "small-world" architecture which is optimized towards a balance of local organization and global integration.[24,27,28] Small-worldness organization of brain networks might hold important benefits, such as high degree of global short communication with relatively few connections.[29,30]

Clinically, patients with schizophrenia exhibit significant changes in their brain network organization as indicated by graph-analytical measures of global short communication paths,[31–33] local organization,[34–36] and small-worldness.[36–43] These domains of investigation have also been linked by the findings indicating that degree of large-scale brain network changes in schizophrenic patients is related to their decline in cognitive functioning.[40–43] Also, the relevance of functional network organization to schizophrenia is indicated by studies showing association between graph analytic measures and cognitive functioning in healthy individuals, such as working memory performance[44] and the intelligence quotient.[45–47]

In summary, multiple studies indicate that graph-analysis is a useful tool to describe changes of global network organization of brain connectivity in patients with schizophrenia. However, meta-analytic investigations are required to evaluate the consistency of results across studies as well as the potentially moderating effects of clinical and methodological factors. This is a critical aim because it will inform current theory and drive future research of the pathophysiology of the disorder. In this study we conducted a comprehensive meta-analysis of all available neuroimaging studies using graph-analysis to investigate functional brain network changes in patients with schizophrenia across modalities (ie, EEG and fMRI).

Methods

Search and Selection Strategy

A comprehensive literature search was conducted in the PubMed database to include all published studies until August 01, 2015. Initially studies were screened using the following search term: ("graph analysis" OR "graph-analysis" OR "small-worldness" OR "small worldness" OR "clustering" OR "path length" OR "global efficiency" OR "local efficiency" OR "modularity" OR "assortativity") AND ("magnetic resonance imaging" OR "MRI" OR "fMRI" OR "resting-state" OR "resting state" OR "EEG" OR "electroencephalography" OR "MEG" OR "magnetic encephalography") AND ("schizophrenia" OR "schizophreniform" OR "psychosis" OR "psychotic"). To be included in the meta-analysis, studies needed to report graph-analytical measures (small-worldness, clustering coefficient, minimal path length, global efficiency, local efficiency) of brain networks in healthy control subjects and patients with schizophrenia or schizophreniform disorder as diagnosed by the DSM-IV.[48] Studies were required to report sufficient statistics to allow the computation of an effect size quantifying group differences. Even though the source of the measured signal is fundamentally different between MRI-based and electrophysiological measures (EEG, MEG), studies of all modalities studies were included as in both cases data is typically modeled under the assumption that what is measured is the same (neural activity).

Data Extraction

The main outcome measure extracted from the individual studies was the standardized mean difference (Hedges' g[49]) describing differences between healthy control subjects and patients with schizophrenia. If data was not available in the published manuscripts to calculate effect sizes of group differences, authors were contacted via email and asked to provide the additional information. If no data was available upon request, data was obtained using the "webplotdigitizer" software (www.webplotdigitizer.org[50]). This allowed the computer-guided extraction data in the form of means and measures of dispersion (eg, standard error of mean, confidence intervals) from published figures. This approach has previously been employed successfully by multiple studies.[51] Otherwise, if no sufficient data was available to calculate effect sizes, studies were excluded from the meta-analysis. If studies reported multiple comparisons for the same graph-analytical measure (eg, for different thresholds or for different frequency bands in case of EEG studies), effect sizes were averaged across all reported comparisons. If a study reported multiple measures of global short communication paths or local organization, effect sizes for these measures from this study were averaged. In order to avoid bias we excluded samples from the same neuroimaging modality with large overlap (shared $n > 20\%$).

Data Analysis

For every study included in the analysis, Hedges' g was calculated and entered into a random-effects meta-analytic model.[49,52] The summary effect sizes across all studies were computed using a restricted maximum-likelihood estimator.[53] As a first step, functional studies were analyzed by combining all modalities. Subsequently, further analyses were employed separately for EEG and fMRI studies, as well as for studies at rest and during task performance. Heterogeneity was assessed via the I^2 value which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[54] I^2 values of 25%, 50%, and 75% can be interpreted as indicating low, moderate, and high heterogeneity respectively.[54] A significance level of $P < .05$ (2-tailed) was used for all analyses. The potential moderating effects of publication year, gender, and the age of subjects was evaluated using meta-regression.[49] Publication bias was assessed by visual inspection of funnel plots and by employing Egger's test for funnel plot asymmetry[55] for every separate meta-analysis. All statistical analyses were conducted using the R statistical programming language version 2.10.1[56] with the package "metafor."[57]

Results

The literature search identified $n = 161$ potential studies. After study selection using the predefined exclusion criteria, $n = 8$ fMRI studies[34–38,58–60] (patients: $n = 218$, age = 26.7 years; controls: $n = 235$, age = 26.5 years) and $n = 5$ EEG studies[43,61–64] (patients: $n = 137$, age=28.2 years; controls: $n = 78$, age = 27.6 years) were included in the meta-analysis. All studies included samples of patients diagnosed with schizophrenia according to the DSM-IV.

The meta-analysis of all studies reporting measures of networks' global short communication paths (minimal path length or global efficiency) showed no significant change in patients with schizophrenia ($g = 0.26$, $k = 12$ studies, $z = 1$, $P = .32$, 95% CI: −0.25 to 0.77; heterogeneity: $I^2 = 89.71\%$, 95% CI: 79.28 to 96.35%, figure 1). There was no effect of potential moderators such as year of publication, age of patients, age of controls or gender ratio (all $P > .1$). Similarly, there was no significant effect in the subanalysis of EEG studies during task ($g = -0.16$, $k = 4$ studies, $z = -0.76$, $P = .45$, 95% CI: −0.58 to 0.26; heterogeneity: $I^2 = 49.2\%$, 95% CI: 0 to 96.44%), fMRI studies at rest ($g = 0.63$, $k = 5$ studies, $z = 1.04$, $P = .3$, 95% CI: −0.56 to 1.82; heterogeneity: $I^2 = 94.62\%$, 95% CI: 84.98 to 99.34%), or fMRI studies during task (Fornito et al[38], 2011: $g = 0.06$, 95% CI: −0.51 to 0.62; He et al[59], 2012: $g = 0.1$, 95% CI: −0.46 to 0.48; Ma et al[58], 2012: $g = -0.05$, 95% CI: −0.57 to 0.48). For the EEG studies at rest 2 studies reported a nonsignificant decrease of minimal path length in patients (Jhung et al[61], 2013: $g = -0.29$, 95% CI: −0.98 to 0.39; Micheloyannis et al[62], 2006: $g = -0.63$, 95% CI: −1.27 to 0.01) whereas 1 study reported a significant increase in patients (Rubinov et al[63], 2009: $g = 0.53$, 95% CI: 0.08 to 0.97).

The meta-analysis of all studies reporting measures of local organization (clustering coefficient or local efficiency) indicated a significant reduction in patients with schizophrenia ($g = -0.56$, $k = 12$ studies, $z = -2.3$, $P = .02$, 95% CI: −1.04 to −0.08; heterogeneity: $I^2 = 88.24\%$, 95% CI: 76.24 to 95.83%, figure 1) with no evidence for a publication bias ($z = 0.04$, $P = .96$). There was no effect of potential moderators such as year of publication, age of patients, age of controls or gender ratio (all $P > .1$). This effect was also apparent in the subanalysis of fMRI studies at rest ($g = -1.33$, $k = 7$ studies, $z = -5.39$, $P < .001$, 95% CI: −1.81 to −0.85; heterogeneity: $I^2 = 73.43\%$, 95% CI: 38.63 to 92.92%) with no evidence for a publication bias ($z = 1.15$, $P = .25$). For EEG studies at rest 1 study reported a significant decrease in the clustering coefficient in patients (Micheloyannis et al[62], 2006: $g = -0.74$, 95% CI: −1.37 to −0.10) and 2 studies reported a no significant change (Jhung et al[61], 2013: $g = 0.1$, 95% CI: −0.58 to 0.77; Rubinov et al[63], 2009: $g = -0.46$, 95% CI: −0.91 to −0.02). Similarly for EEG studies 1 study reported a decrease in the clustering coefficient in patients (Micheloyannis et al[62], 2006: $g = -0.64$, 95% CI: −1.27 to −0.01) and 2 studies reported no significant change (Shim et al[43], 2014: $g = -0.3$, 95% CI: −0.77 to 0.18; Jhung et al[61], 2013: $g = 0.28$, 95% CI: −0.40 to 0.96). All 3 available studies of fMRI during task indicated no change in measures of local organization in patients (Fornito et al[38], 2011: $g = 0.14$, 95% CI: −0.43 to 0.71; He et al[59], 2012: $g = -0.02$, 95% CI: −0.50 to 0.44; Ma et al[58], 2012: $g = 0.07$, 95% CI: −0.45 to 0.59).

In the meta-analysis of all studies reporting small-worldness, there was evidence for a significant decrease in patients with schizophrenia compared to healthy controls ($g = -0.65$, $k = 5$ studies, $z = -2.71$, $P = .01$, 95% CI: −1.12 to −0.18; heterogeneity: $I^2 = 68.73\%$, 95% CI: 15.93 to 95.73%, figure 1) with no evidence for a publication bias ($z = 0.22$, $P = .83$). This effect was not affected by potential moderators such as year of publication, age of patients, age of controls or gender ratio (all $P > .1$). All 3 available studies of fMRI at rest reported a significant decrease of small-worldness in patients (Lynall et al[34], 2010: $g = -0.91$, 95% CI: −1.71 to −0.11; Alexander-Bloch et al[37], 2013: $g = -0.68$, 95% CI: −1.33 to −0.03; Tomasi et al[36], 2014: $g = -1.07$, 95% CI: −1.42 to −0.72). The only study that investigated small-worldness in patients during task did not report a significant decrease (Fornito et al[38], 2011: $g = 0.19$, 95% CI: −0.37 to 0.76). The only available EEG study indicated that small-worldness in patients at rest is similar to healthy controls (Jhung et al[61], 2013: $g = -0.33$, 95% CI: −1.01 to 0.36), whereas during task there seems to be a reduction in small-worldness (Jhung et al[61], 2013: $g = -1.32$, 95% CI: −2.06 to −0.57).

Discussion

Extant literature includes comprehensive reviews of brain functional changes in schizophrenia.[22] However, in the present meta-analysis the effect of network changes in schizophrenia are quantified and analyzed with respect to their consistency across studies. Our results suggest a significant reduction in local organization of brain networks in patients with schizophrenia with a moderate effect size ($g = -0.56$). This effect was robust with respect to the inclusion of potential confounding variables and there was no evidence for a publication bias. Also, schizophrenia was also associated with a lower degree of small-worldness organization with a moderate effect size ($g = -0.65$). In contrast, measures of global short communication paths indicated no change in functional brain networks of patients. However, it is important to note that the number of available studies investigating brain network architecture in schizophrenia is still small so results need to be interpreted with care.

Local Organization of Brain Networks in Patients With Schizophrenia

In the present meta-analysis 2 measures of network local organization were investigated: the clustering coefficient and local efficiency. A functional network architecture with high local organization allows efficient computation at a local level in functionally specialized regions. At the same time, such networks are also robust to node failure. In case of damage to a local node, the high within-cluster connectivity enables the network to preserve its functionality. High local organization in brain networks has been associated with higher cognitive performance in tasks of attention, memory, executive functions, and psychomotor speed.[34,59,65–67] Interestingly, local organization of brain networks in schizophrenic patients might be a predictor of future decline of intelligence scores and increase of psychotic symptoms.[68] Also, in patients with schizophrenia reduced local organization is related to more severe psychotic symptoms as measured by Positive and Negative Syndrome Scale (PANSS),[60,69] in particular with the cognitive subscales.[43] Interestingly, in our analysis the reductions in network local organization were most pronounced in resting-state fMRI studies when compared to those using a task design. One potential hypothesis for this finding is that differences in brain network organization detected in task-based fMRI are affected by individuals' task performance[70] and thus are associated with additional heterogeneity. In summary, there is evidence for a reduction of local organization in brain networks of patients with schizophrenia and multiple reports indicate that reduced network local organization might relate to the cognitive and clinical symptoms[43,60,69] seen in patients with schizophrenia.

Global Short Communication Paths in Brain Networks of Patients With Schizophrenia

In the present meta-analysis 2 mathematically related metrics of brain networks' global short communication paths were investigated: functional minimal path

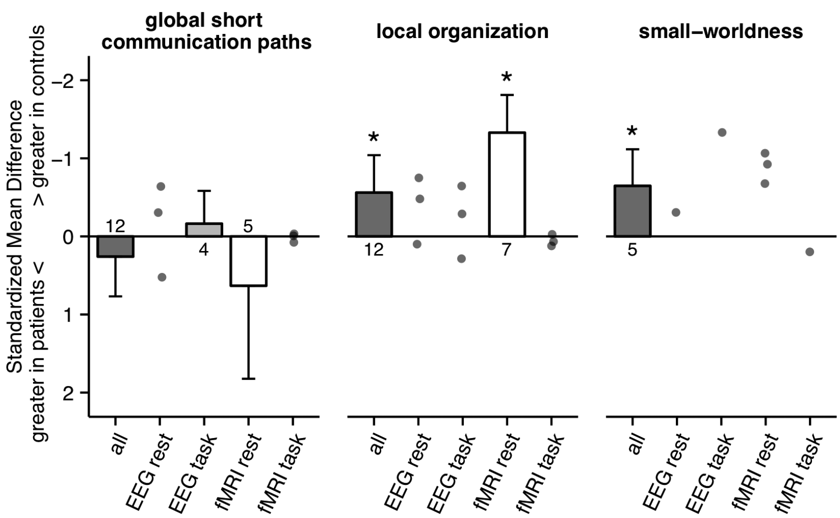

Fig. 1. Effect sizes of studies reporting changes in functional brain networks in patients with schizophrenia as indicated by measures of global short communication paths (minimal path length, global efficiency), local organization (clustering coefficient, local efficiency) and small-worldness. Summary effect sizes of meta-analyses are presented for cases with $n \geq 4$ using bar plots and individual studies' effect sizes are plotted as single points. For each meta-analysis the number of available studies is indicated below each bar plot. Negative values on the y-axis represent lower graph-analytical parameters for patients compared to healthy controls. Error-bars represent the upper bound of the 95% CI. *Indicates significance on the level of $P < .05$.

length and global efficiency. Global short communication paths of a network are a critical feature of efficient network architecture as this organization allows the rapid transfer of information across the network. Thus, multiple studies report that individuals with highly expressed global short communications paths also show superior performance in tests of general intelligence[45–47] as well as attention and verbal memory.[67] Overall, in functional brain networks 2 measures of global short communication paths (global efficiency, minimal path length) indicated no change in patients with schizophrenia. However, some studies indicated that minimal path length is related to the cognitive symptoms in schizophrenic patients[43] and structural studies examining changes in anatomical wiring of brain networks in schizophrenia have noted strong reductions in global communication paths.[22,41,71,72] Also, the severity of psychotic symptoms correlated with graph analytical measures of brain networks' integration.[58,60,63,69] However, it needs to be noted that the 2 investigated measures (minimal path length, global efficiency) might only partially capture the amount of network integration.[73,74] Thus alternative measures of integration might be more sensitive to investigate organizational changes of brain networks in patients with schizophrenia.

Small-Worldness Architecture in Patients With Schizophrenia

In general, functional small-worldness properties have been reported in a multitude of various networks suggesting important advantages associated with this organization.[28] Specifically, small-worldness represents an optimized trade-off between local organization into functionally specialized modules and global communication. Deviations from this optimum might result in reduced computational efficiency. While there has only been 1 study that has reported a direct association between reduced small-worldness and cognitive functioning in schizophrenia,[59] others report associations of graph-analytical measures with positive and negative symptoms.[60,69] Specifically, Wang et al[69] report that PANSS positive and negative scores of patients were related to both local and global connectivity measures. Additionally, reduced small-worldness in healthy controls is associated with lower cognitive functioning in domains usually associated with schizophrenia, including memory, attention, executive functioning, and psychomotor speed.[34,43,65] Combined, these results suggest that small-worldness may be implicated in the functional deficits and symptoms seen in schizophrenia, although more research is required to support this hypothesis.

Limitations

There are a large number of methodological factors in the analysis of neuroimaging data that most likely have an effect on graph-analytical measures and potentially on the effect size reported in the present meta-analysis. As an example, there are a variety of methods for determining statistical significance of connectivity differences between groups[75] or different ranges of thresholds for determining networks (see table 1, "Thresholding"), which can affect the effect size of the findings and thus introduce heterogeneity of results into subsequent meta-analyses. Also, some studies calculated graph-measures that were normalized with respect to random networks generated by randomly rewiring connectivity matrices, while other studies did not implement such normalization what may have also contributed to the heterogeneity in the present meta-analysis. These methodological differences likely reflect the infancy of graph analytical analyses, which is addressed in comprehensive discussion elsewhere (see Fallani et al[75] for a review and Fornito et al[76] for detailed discussion).

Another limitation is that exposure to antipsychotic medication is a potentially important moderator of global brain network changes in schizophrenia, but this was not addressed in this meta-analysis. Antipsychotics have been shown to affect results in neuroimaging studies of schizophrenia in different modalitiew.[1,6,63,77] However, most graph-analytical structural[78] and functional[34,43] neuroimaging studies report no effect of antipsychotic medication. Additionally, Zhang et al[32] report changes in structural network organization in drug-naïve patients. As such, it is unlikely that the results of the present study could only be explained by the effect of antipsychotic medication. Unfortunately, most studies included in the present analysis did not report a quantitative measure of current or previous antipsychotic medication (eg, chlorpromazine equivalent measures) that could have been investigated. This represents a methodological shortcoming of the current graph-analytical literature of schizophrenia that needs to be addressed in future research.

Finally, it needs to be noted that some studies report reduced overall connectivity in patients with schizophrenia.[9] Typically, reduced overall connectivity in brain networks is associated with reductions in measures of local organization. However, few of the studies included in the present analysis reported a measure of overall connectivity strength, which precluded any analysis of this potential moderator variable. Future studies should address the interplay of overall connectivity changes and specific alterations of network architecture in patients with schizophrenia.

Future Directions

A central question for future investigations is whether differences in functional brain network architecture represent vulnerability traits and are already present in subjects at genetic[79] or clinical[80] risk for schizophrenia, or whether these differences are more related to the current

Table 1. Overview of All Samples Included in the Meta-analysis

Study	Year	Modality	*n*	Age	Males (*n*)	*n*	Age	Males (*n*)	Condition	Reported Graph-Analytical Measures	Statistical Dependency Measure	Connectivity Matrix	Thresholding
Micheloyannis et al[62]	2006	EEG	20	32.4	15	20	27.4	15	Rest	Clustering coefficient, minimal path length	Synchronization likelihood	Binary	Absolute
Rubinov et al[63]	2009	EEG	40	19.6	26	40	19.7	26	Rest	Clustering coefficient, minimal path length	Nonlinear interdependence	Weighted	Relative (10%–20%)
Fogelson et al[64]	2013	EEG	20	35.5	18	20	36.2	18	Task	Minimal path length	Synchronization likelihood	Binary	Relative (8%–15%)
Jhung et al[61]	2013	EEG	23	19.6	5	13	20.2	5	Task & rest	Clustering coefficient, minimal path length, small-worldness	Synchronization likelihood	Binary	Relative
Shim et al[43]	2014	EEG	34	33.9	14	34	34.7	20	Task	Clustering coefficient, minimal path length	Phase locking value	Weighted	None
Lynall et al[34]	2010	fMRI	12	10.0	33	15	14.0	33	Rest	Average clustering, small-worldness, global efficiency	Wavelet correlation	Binary	Relative (37%–50%)
Alexander-Bloch et al[35]	2010	fMRI	13	18.0	5	19	19.0	9	Rest	Clustering coefficient, global efficiency, local efficiency	Wavelet correlation	Binary	Relative (30%–50%)
Yu et al[60]	2011	fMRI	19	36.5	15	19	33.9	9	Rest	Clustering coefficient, minimal path length, global efficiency, local efficiency	Partial correlation, z-transformed	Binary	Relative (35%–43%)
Fornito et al[38]	2011	fMRI	23	20.5	14	25	22.1	13	Task	Clustering coefficient, minimal path length, small-worldness, global efficiency, local efficiendy	Beta series correlation	Binary	Relative (5%–45%)
Ma et al[58]	2012	fMRI	28	37.8	23	28	32.7	19	Task & rest	Clustering coefficient, minimal path length	Normalized mutual information	Binary	Absolute
He et al[59]	2012	fMRI	35	34.3	26	35	34.6	27	Task	Clustering coefficient, minimal path length, global efficiency, local efficiency	Partial correlation, z-transformed	Binary	Relative (19%–34%)
Alexander-Bloch et al[37]	2013	fMRI	19	18.7	9	20	19.4	10	Rest	Clustering coefficient, small-worldness	Wavelet correlation	Binary	Relative (1%–10%)
Tomasi et al[36]	2014	fMRI	69	38.0	55	74	36.0	51	Rest	Clustering coefficient, minimal path length, small-worldness	Correlation	Binary	Relative (40%–65%)

Note: EEG, electroencephalography; fMRI, functional magnetic resonance imaging.

clinical symptoms of patients. Also, more studies are needed to investigate the relationship between task- and rest-associated network organization. As such, future studies could investigate the longitudinal course and stability of the differences found here. Additionally, it has been suggested that structural and functional brain connectivity can be altered by meditation,[81,82] pharmacological treatment,[83] or physical exercise[84] that reduce symptoms and improve outcomes. Given the sensitivity of measures of brain functional connectivity to treatment interventions, as well as their role for cognition in psychiatric disorders, future studies need to investigate the potential of graph-analytical parameters to monitor improvements in cognition following interventions[85] in addition to their use as biomarkers for classification of psychiatric disorders.[86]

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