Brain Network Topology Maps the Dysfunctional Substrate of Cognitive Processes in Schizophrenia

Rossana Mastrandrea1, Fabrizio Piras2, Andrea Gabrielli*3,1, Guido Caldarelli1,3, Gianfranco Spalletta2,4, and Tommaso Gili1

1IMT School for Advanced Studies, Lucca, Piazza S. Francesco 19, 55100 Lucca, Italy
2Istituto dei Sistemi Complessi (ISC) - CNR, UoS Sapienza, Dipartimento di Fisica, Università “Sapienza”; P.le Aldo Moro 5, 00185 - Rome, Italy
3IRCCS Fondazione Santa Lucia, Via Ardeatina 305, 00179 Rome, Italy
4Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Tx, USA

Abstract

Current understanding of schizophrenia associates this disorder with alterations in the functional organization of the brain. Resting-state functional connectivity studies have tried to characterize global and local changes induced by this mental illness, but failed to model symptoms expression exhaustively. Recently, network neuroscience, a branch of neuroscience that derives its tools of investigation from graph theory, shed some light on the functional and structural modifications occurring to the brain that can give rise to the recognized symptomatology of schizophrenia. Nonetheless, the existence of clear links between resting-state dysfunctional connectivity and symptoms is still under debate. Using a novel network analysis of spontaneous low-frequency functional MRI data recorded at rest, we study the “functional network” that describes the extent of synchronization among different areas of the brain. Comparing forty-four medicated patients and forty healthy subjects, we detected significant differences in the robustness of these functional networks. Such differences resulted in a larger resistance to edge removal (disconnection) in the graph of schizophrenic patients as compared to healthy controls.

This paper shows that the distribution of connectivity strength among brain regions is spatially more homogeneous in schizophrenic patients with respect to healthy ones. As a consequence, the precise hierarchical modularity of healthy brains is crumbled in schizophrenic ones, making possible a peculiar arrangement of region-to-region interaction that, in turns, produces several topologically equivalent backbones of the whole functional brain network. We hypothesize that the manifold nature of the basal scheme of functional organization within the brain, together with its altered hierarchical modularity, contributes to positive symptoms of schizophrenia. Our work also fits the disconnection hypothesis that describes schizophrenia as a brain disorder, characterized by abnormal functional integration among brain regions.

*Corresponding Author: andrea.gabrielli@roma1.infn.it
Introduction

The human brain is a complex system characterized by the interaction of populations of neurons and individual brain regions, whose functioning can be modelled by multi-scale topological entities as complex networks [1]. The functional architecture of the human brain and in particular its network nature have become a point of attraction for the interest of the neuroscientific community, mainly because of its potential to improve our understanding of human cognition, and its alteration in neurological disease and psychiatric disorders [2, 3]. Specifically, the investigation of the functional organization of the brain, as obtained by resting state functional magnetic resonance imaging (rs-fMRI), has revealed differences in brain network topology in a number of psychiatric disorders including schizophrenia [4, 5, 6, 7, 8], bipolar disorder [9, 10] and attention deficit hyperactivity disorder (ADHD) [11, 12]. Although, among these, schizophrenia has received the greatest attention, its pathophysiology remains particularly elusive. Previous theoretical and empirical frameworks described the disorder as circumscribed alterations in neural circuits [13]. A different hypothesis suggested that main aspects of symptoms and the associated cognitive alterations arise from a deficit in the functional integration of distributed brain networks leading to aberrant interactions between brain regions also referred as “dysconnection” syndrome [14]. This hypothesis is based on experimental evidences, which suggest that in normal brains functional interactions between distributed neuronal ensembles are critical for the production of coherent action and cognition [15, 16]. The synchronization of neuronal activity that could induce effective coordination of information processing is a mechanism to reach such interactions [17, 18, 19]. Indeed, synaptic pruning has been also hypothesized to underlie the neuropathology of schizophrenia [20]. It has been showed that neural networks in the brain are formed during development using a pruning process that includes expansive growth of synapses followed by activity-dependent elimination [21, 22]. An abnormal increase in synaptic pruning generally implies that a normal complement of synapses is formed during development followed by an excess of elimination [23].

Brain intrinsic functional connectivity, captured by rs-fMRI [24, 25], has shown alterations in specific genetically controlled neural circuits in schizophrenia [26, 27, 28], and evidenced the variability associated with this neuropsychiatric illness [29, 30, 31]. Since it reduced also performance confounds in schizophrenia with cognitive deficits, it has been widely used as a tool to predict disease states [32, 33, 34, 35]. Changes in global (whole brain) functional connectivity have also been found in some studies [7, 29, 36]. Recently network neuroscience [2, 37], the application of graph theory [38, 39] to the study of brain networks, highlighted in schizophrenia patients more widespread disturbances in the dynamics of large-scale brain networks [7, 40, 41, 42, 43], and the alterations of the modular structure of the whole system [44, 45]. Although great efforts have been devoted to the understanding of the basic processes underlying schizophrenia, and diverse attractive hypotheses have been proposed, a unified description of the possible sources at the base of the symptoms associated with such a serious mental illness is still under debate. A possible explanation may stem from the consideration according to which the heterogeneity in findings may be due to the fact that cognitive dysfunctions contribute to the alteration of functional connectivity [34], passing through the symptoms in a sort of feed-back process. In this paper, we investigated the alteration of the hierarchical participation of brain regions to the whole network as a function of the weights assigned to the links among them [46]. The strength of correlation between the time-series of the intrinsic neural activity from two regions, as measured by rs-fMRI, was considered the weight of the link joining them. We hypothesized that the altered topology of functional brain networks in schizophrenia is characterized by an unbalance of strong and weak weights among areas belonging both to systems highly engaged in the same processing roles and to other with different processing assignments [7]. This implies that a possible source of symptoms may arise from a sub-optimal optimization of the network arrangement as a consequence of such an altered distribution.
of functional connections. By means of the maximum spanning tree (MST) representation \[46\] we show, for the first time, that not only a disruption of the local modular organization happens in the illness, as consequence of the reshuffling of significant connections across the whole network, but that it leads to the existence of several topologically equivalent MSTs in schizophrenia. Moreover, the analysis of the percolation curves \[46\] from healthy and diseased functional brain networks showed that the region-to-region interaction is more resistant to disconnection in patients than in healthy subjects, allowing a more persistent giant component size in schizophrenia. This implies a lack of hierarchical specialization in the functional connectivity patterns of the brain and the loss of higher levels of cortical hierarchies that generate predictions of representations in lower levels. The ability to resolve these changes by looking at the multiple scales of the possible interactions among brain regions sheds new light on the functional implications of aberrant functional connectivity in schizophrenia.

**Results**

**Inter-subject variability**

The inter-subject variability for the group of healthy subjects (HTH) has been explored in a previous work \[46\], finding a high level of homogeneity to justify the choice of focusing on the human functional “average brain”, computed as the mean of all the forty individual correlation matrices. Here, we repeated the same analysis for the group of schizophrenic subjects (SCZ).

In fig. 1 we report the average correlation values and the related standard deviations computed for each pair of brain areas over the forty-four individuals. The resulting correlation matrix has been thresholded using the false discovery rate: in this way average values close to zero have been neglected. Indeed, their presence could be due to: (i) extremely weak functional correlations between brain regions for most of subjects in the sample; (ii) fluctuations between positive and negative values over the forty-four subjects such that the final average results close to zero. Both cases are not interesting as the former would not add any relevant information to the study of the functional network architecture, while the latter could be ascribed to acquisition problems introducing biases in the study. Indeed, the debate on the meaning of negative correlation values in fMRI studies is still open \[47\] without a general consensus militating in favour of their inclusion or exclusion in the analysis. We think they do not bring any relevant information to the scope of the actual study, therefore from now on, we will always refer to the squared correlation values \[48\] focusing on the intensity of connection rather than its sign.

Results showed in fig. 1 and particularly the coefficient of variation (fig. 1c), suggest that the group of SCZ is characterized by a level of heterogeneity much larger than the one observed for HTH \[46\]. This outcome makes meaningless the analysis of an “average brain” of SCZ. Therefore, in what follows we will perform a subject-wise study, then we will show the average and the 95% confidence interval of the main quantities analyzed.

**Subjectwise Percolation Analysis**

We performed a subject-wise percolation analysis for the two group of individuals. Given the individual correlation matrix, its entries were squared and ranked in ascending order. One at a time the link corresponding to the actual correlation value in the list was removed by deleting it from the rank. The number of connected components was evaluated step by step after each link removal. This enabled us to calculate the number of connected components in the remaining graph by systematically varying the threshold on the network. The procedure was iterated across subjects, and finally the average percolation curve was computed for the two groups (HTH and SCZ) and
Figure 1: **Inter-subjects variability.** (a) Mean, (b) standard deviation and (c) coefficient of variation of pairwise correlation values computed over the 44 schizophrenic patients involved in the study.

reported in figure 2(a) together with the 95% confidence interval.

A clear separation emerges between the average percolation curves of the two groups of individuals. Specifically, the functional brain network in SCZ appears more resistant to the disaggregation process due to the removal of weak links. The number of connected components remains smaller than for the HTH case, revealing a general slower decomposition process of the global network architecture. Similar considerations come from figures 2 (b)-(c) showing the variation in the size of the giant component as the threshold value increases. Indeed, there is a clear delay in the emergence of the second connected component for all schizophrenic subjects with respect to healthy individuals.

Firstly, we checked if such differences in the percolated networks could be ascribed to significant differences in the distribution of network edge-weights. For this reason, in figure 3 we show the distribution of the correlation values describing the functional brain networks of all subjects in the two groups pooled together (squared values in the inset). Even if the distribution of weights collected from the Schizophrenic patients is clearly wider than the one coming from healthy subjects, when we consider squared correlation values, they appear very similar. Hence, there are not significant differences between the two weights distribution to explain the observed delay in the decomposition of the percolated network of Schizophrenic patients with respect to healthy subjects. On the contrary, if we compare how the degree of each ROI change at each threshold value (on average), we discover relevant deviations between the two groups (fig.4). Indeed, in the case of Schizophrenic patients, the decrease of node degree appears quite homogeneous for all ROIs. In other terms, fig.4 reveals that during the percolation weak links are removed almost ‘randomly’ from the functional brain network of schizophrenic patients, with the consequence of affecting almost in the same way the variation of the degree of each ROI; while in the HTH case there are nodes disconnecting rapidly from the rest of the network and becoming soon isolated nodes, i.e. new disconnected components, and viceversa for a small number of brain regions. This result suggests that weaker links are uniformly distributed in the functional brain network of patients instead of being concentrated around the same node or groups of nodes as for the healthy subjects. Such important consideration could not come from the simple observation of weights distributions in fig.3 as it would suggest by contrast a similar behaviour of the percolated networks. On the contrary, fig.4 (b), with ROIs reordered according to the average degree over the whole percolation, clearly highlights the presence of nodes connected to the network mainly by weak links in HTH with respect to SCZ case. It is worth to notice that if we group ROIs in order to have 8 macro-regions according to the anatomical localization and specific functioning of brain areas (Supplementary for details) and in each of them we still reorder nodes looking at the average degree over the whole percolation, we find that there is high heterogeneity...
in each group (fig. 5), especially in the Cerebellum, Frontal Lobe and Deep Grey Matter regions containing the nodes with the weakest correlation values with all the other brain areas. On the other hand, the Occipital Lobe, Insula and Parietal Lobe contain the ROIs resisting more to the disconnection process induced by the percolation. Evidently, we lose such important information if we look at the same figure for the Schizophrenic patients.

![Percolation Analysis](image)

**Size of the giant component**

Figure 2: **Percolation Analysis.** Top: (a) number of connected components of the percolated network versus the related correlation threshold. The two curves represent the average of the individual percolation curves and are reported together with the 95% confidence interval. Bottom: size of the giant component in each percolated network versus the related correlation threshold for all (b) healthy subjects and (c) schizophrenic patients.
Subjectwise Maximum Spanning Tree

The percolation analysis highlights the existence of a non trivial functional organization of the human brain network with an evident difference between the groups of HTH and SCZ. Here, to investigate more on this aspect we built the Maximum Spanning Tree (MST) associated to the correlation matrix of each subject separately [46]. Similarly to what observed for HTH, also in SCZ, the MSTs exhibit a chain-like functional organization of brain regions. A way to easily check it for each subject consisted in looking at the node degree distribution: the abundance of degrees equal to 1 and 2 and the relatively small maximum values confirm the result (figure available upon request).

The node degree distribution does not provide any relevant differential information about the functional network topology of the two groups. We aimed to define a quantitative measure able to establish if subtle changes occurred to the network. To this purpose we introduced the allometric scale, a quantity widely used for measuring the fractal nature of rivers, vascular systems, foodwebs [49, 50].

Given a directed spanning tree of a network it is possible to assign to each node two quantities, one proportional to the amount of resources exchanged at that node, and the other related with the cost of such transfer (see Methods). It has been observed that there exists a power-law relation between these two quantities, with the exponent being universally identified for river and vascular networks [49]. These power-law relations are usually called allometric. They describe how the topological properties scale with network size, and are related to the self-similarity of the tree-like structure: they signal that the structure of the whole tree is statistically equivalent to that of any of its branches/subtree. In general, the allometric scale, $\eta$, ranges between 1 and 2, where $\eta \to 1$ in a star-like tree and $\eta = 2$ in a chain-like tree. Thus, values of $\eta$ close to 1 (2) mean a global star-like (chain-like) structure of the whole tree and its branches.

The MSTs associated to the human functional brain networks in this paper are undirected by construction. Thus, we introduced a directionality in order to compute the aforementioned quantities, $(A_i, C_i)$, for each node. To avoid any arbitrary choice, we considered all nodes as root, associating to each subject 116 directed MSTs (Methods). In figure 6(a)-(e) we show an example.
of such procedure with a toy model tree consisting of 10 nodes and 3 (over 10) possible its directed versions when nodes 5, 7 and 1 are respectively chosen as roots. Moreover, we report in fig.6(c) the MST of the human functional brain network of a randomly chosen subject indicating one possible root and the induced directionality on the MST (fig.6(e)).

Once we have associated to each node the two quantities, \((A_i, C_i)\), we computed the slope, \(\eta\), of the power law fit for the distributions of \(A_i\) and \(C_i\). This procedure was repeated separately for each HTH and SCZ, and the resulting \(\eta\) values were averaged across subjects and reported with the 95% confidence interval in figure 7.

The mean of allometric slopes for the two groups resulted very close (fig.7), revealing on average a similar chain-like organization (shown in [46] for healthy subjects only) of the functional brain network backbone for both HTH and SCZ. Furthermore, it is worth to notice that the allometric scale is on average \(\sim 1.5\), between the two extreme values reachable by \(\eta\), militating in favour of a system whose skeleton seems to balance efficiency and cost. In order to investigate more on the differences found by means of the percolation analysis (i.e. a widespread change of connectivity strength, i.e. correlation coefficient, distributions in schizophrenia networks with respect to the...
healthy ones), we introduced a novel procedure. Specifically, we considered higher rank MSTs as it follows: if we define the MST of a given network as a first rank MST, we can consider the second (third, fourth, and so on) MST simply computing the maximum spanning tree of the considered network, once all links corresponding to the first (second, third, and so on) MST have been removed from it. We computed for each subject in each group the first four rank MSTs and reported the allometric slopes averaged over all subjects in the two groups, together with their 95% confidence intervals.

Results show that, starting from a similar condition (fig8), allometric slopes tend to reduce as the MST rank increases. However, the different speed of reduction determines an evident and growing difference between the two groups of subjects, with the allometric slope decreasing more slowly for SCZ than HTH.

**Discussion**

Differences in brain functional architecture between people suffering from schizophrenia and healthy individuals are as vast as subtle ([4, 30]. Great efforts have been made for the experimental characterization of the disorder, from the molecular ([51, 52, 53, 54, 55, 56, 57]) to the mesoscopic scale ([58, 59, 60, 61, 3, 62]). In this paper we presented the results of a network-based analysis of fMRI data recorded at rest in schizophrenic patients and healthy subjects. Our aim was to assess
Figure 1: Percolation analysis. Largest component size (color) for each subject (y-axis) and each correlation value (x-axis). The correlation values on the x-axis are exactly the same for the two groups since we merged the ones corresponding to all healthy and schizophrenic subjects (if a specific correlation value is not present in the correlation matrix of a subject, we simply report the size component related to the previous one present in such subject).

Figure 1: MST characterization.

Figure 6: Allometric scale example. (a) Toy model tree of 10 nodes. It is possible to obtain 10 directed version of the undirected tree in (a), according to the different node chosen as root. (b)-(d) three directed version of the tree in (a) with roots equal to, respectively, nodes 5, 7 and 1. Numbers in brackets represent the quantities \((A_i, C_i)\) associated to each node. (e) Maximum spanning tree of the human functional brain network of an individual chosen at random in the group of healthy subjects with directionality induced by the choice of node fifty-one as root. Colors in (e) represent anatomical regions according to the grouping of AAL parcellation shown on the right bottom: • Frontal Lobe; • Insula; • Cingulate; • Temporal Lobe; • Occipital Lobe; • Parietal Lobe; • Deep Grey Matter; • Cerebellum.

The basal structure of the cerebral functional network and the possible alterations induced by the illness. A percolation and a Maximal Spanning Tree (MST) analysis were implemented \([63, 46]\) for the two cohorts of subjects. Our findings demonstrate a global change of the connectivity strength (i.e. the correlation coefficient) distribution in patients’ functional networks as compared to healthy subjects, which consists in an increased homogeneity of the weighted links distribution.
Figure 7: **Allometric scale: first rank MST.** Exponent of the power law relation between the quantities $A_i$ and $C_i$ computed for the MST of each healthy subject and Schizophrenic patient separately versus the related ROI-root. We reported the average allometric scale for the two groups together with their 95% confidence interval.

in the connectivity intensity pattern across the whole functional network of schizophrenic patients with respect to healthy individuals.

The first evidence of this property comes from the inspection and analysis of the percolation curves obtained from healthy subjects and patients. Schizophrenic functional networks seem to be characterized by a region-to-region interaction more resistant to be disconnected than in healthy subjects. Indeed, by moving the threshold (below which weighted links are erased) from low to high values of connectivity strength, the number of disconnected clusters at a given threshold is systematically smaller in schizophrenic than in healthy subjects (fig.2 (a)). The same process may be argued by comparing the giant component size ([64]) in healthy networks with the same quantity obtained from schizophrenia patients, as a function of the threshold: the size reduction, along with the threshold increase, starts always in healthy subjects first (fig. 2 (b)-(c)). A wider distribution of the connectivity strengths in patients with respect to healthy subjects (see fig.3) cannot explain such differences in the percolated networks, especially because the two distributions become very similar when we focus on squared correlation values (fig.3 inset). On the contrary, an evident discrepancy between the two groups can be found in the distribution of node degree computed for each percolated network (fig. 4 and 5). This outcome sheds lights on the existence of a more homogeneous distribution of connections in the human functional brain network of schizophrenic patients with respect to healthy subjects, responsible for a delayed emergence of a second connected component in the percolated networks.

The modular structure of a network is determined by the unbalance or predominance of inward and outward links of individual communities, rather than by the average total distribution of edge weights. In other words, an effect of the re-arrangement of the weights may result in a progressive loss of hierarchy of functional connections, which, in turns, leads to a modularity alteration or disruption. Modularity structure modifications in schizophrenia patients have been reported as due to changes in community participation of nodes in the somatosensory, subcortical, auditory, default mode, and salience networks ([44]) and as a specific fragmentation of somatosensory cortices...
Nonetheless the regional specificity of the cerebral aberrant functioning in schizophrenia is still under debate. Hypo-connectivity was reported in the olfactory cortex, temporal pole, angular gyrus, parahippocampus, amygdala, caudate, and pallidum. On the other hand, hyperconnectivity was found in the default mode network, in the bilateral striatum, and in the connectivity between the default mode areas and visual and motor regions. These findings witness a widespread remodulation of connectivity in patients with respect to healthy subjects, involving both directions (increases and decreases). This phenomenon substantiates the core of our results: functional brain networks in schizophrenia are characterized by a more homogeneous distribution of weights, where strong correlation patterns and weak ones share the same topology. Analogous conclusion was reached by Bassett et al., who investigated the graph topology in schizophrenia patients responsible for changes in the complexity of the human brain’s activity and connectivity with respect to healthy controls. In addition, our results showed also a regional differentiation in the amount of regional connectivity being the frontal lobe, as well as the deep grey matter (Hippocampus, Amygdala, Caudate nucleus, Putamen, Pallidum and Thalamus) and cerebellum, characterized by a larger connectedness in SCZ than in HCS.

The MST analysis of the functional networks did not show any appreciable main difference by comparing healthy subjects and schizophrenia patients. A quantitative confirmation of this result is given by the allometric exponent calculated from each region of interest as seed across subjects. As derived here, the allometric exponent, which expresses a global property of the tree, is calculated by considering each region of interest r as a possible seed of the tree and it represents the coefficient that joins linearly the logarithm of two transfer quantities: \( \log(A_r) \), that is the amount of resources exchanged at r (i.e. the amount of nodes that form the subtree with node r as root) and \( \log(C_r) \), that is the total cost of a transfer involving r (i.e. the \( A_r \) summation over all the nodes in the subtree with node r as root, including r). The MST has not a specific directionality, however the orientations that allow the definition of possible paths of transfer are simply a consequence of nodes arrangement in the subtree defined by the choice of a specific node as starting root for the calculation of the allometric coefficient. Although we do not claim any strict conclusion about information transfer between brain regions, as our results are based on the hemodynamics associated with large brain regions and the number of subjects investigated is limited, we can guess that the pattern of directionality at each node may represent the effort needed by that node to coordinate and integrate with all the others in the networks. Recently we showed that the null-model associated with the MST of a functional brain network in healthy subjects is characterized by a sort of highly branched configuration: the same configuration characterizes the null-model for the MSTs of schizophrenia patients. This means that MSTs derived from functional brain networks can in principle range between two extreme topologies: the linear configuration (allometric exponent equal to 2), the least efficient with lowest cost of functioning and the star-like organization (allometric exponent that tends to 1), the most efficient but with the highest cost of functioning. The configuration of the MSTs we derived from functional brain networks are associated with an allometric exponent approximately equal to 1.5, a configuration that balances efficiency and cost.

In the context of brain functional connectivity, which involves interaction between regions not necessarily close one to the other, and where the proximity is just a consequence of their synchronization, efficiency and cost are intended as the ability to organize information transfer via a synchronous coordination and the provision of energetic resources that sustain such organization respectively. Since we observed a widespread change of connectivity strengths distribution in schizophrenia brain networks, the first thing we did was to explore the topological properties of the MSTs of increasing rank: the main MST (first rank), the second rank MST
obtained as the maximum spanning tree of the full correlation network once the first rank MST was removed from it, and so on for higher orders. Given a complete graph with N nodes it is always possible to decompose it in at most N/2 MSTs and to elicit the topological properties of trees characterized by weaker connections. Our findings show that by progressively removing MSTs from a functional network, the value of the allometric exponent decreases both in schizophrenia patients and in healthy subjects (see fig.8). However the rate of reduction of the exponent is faster in healthy subjects, leading to a net separation of the two groups at the third rank MST (fig.8(c)). Taken together with the results of the percolation analysis, this finding suggests that not only the hierarchy and modular structure of the functional network are reduced by a broader distribution of the connectivity strengths, but also that in terms of the global integration of brain regions in the whole network, weaker links guarantee the same connection topology shown by the stronger ones in schizophrenia patients ([7]). The higher topological similarity of the MSTs of different rank, observed in schizophrenia patients respect to normal subjects, suggests that while in the latter a given stimulus can engage a single functional connectivity path ([4]), in patients it determines the simultaneous involvement of different ones. A possible explanation of this conclusion can be found in the disconnection hypothesis ([72]) about the relations between the molecular and the neuronal pathophysiology that give rise to schizophrenia and its symptoms and signs. It states that such pathology comes from an abnormal response of the NMDA receptor to specific neuromodulatory receptor activation. A failure of such mechanisms may lead to an inability to modulate the precision of sensory evidence, corresponding to the precision of beliefs about the causes of sensory cues, and consequently to false inference (e.g., hallucinations and delusions) ([72]). Our findings show that, not only a disruption of the local organization of modules (i.e. the somatosensory community) happens in the illness, but also a reshuffling of the strengths may arise from the uniformity of the global connectivity distribution in the whole network. The existence of several topologically equivalent MSTs implies the lack of specificity in the functional connectivity organization of the brain that is actually expected to be hierarchically set up in order to account the right integration for the right functioning. A consequence of this multi-choice configuration is the loss of higher levels of cortical hierarchies that generates predictions of representations in lower levels, jeopardizing the performance of the brain to process sensory information by optimizing explanations for its sensations ([73] [74] [75]).

It is worthwhile to further comment the possible physiological causes for the reduction of heterogeneity and hierarchy in the distribution of correlation strength values observed in patients. In a computational model proposed by Cabral et al. ([76]) it has been showed that the best way to obtain functional networks with topological properties matching those reported experimentally for schizophrenia patients would be by decreasing the strength of excitatory synaptic input between brain areas, as a consequence of a disruption of synaptic mechanisms. At the neurophysiological level, the disconnection hypothesis accounts for such altered mechanisms. ([14]). Nonetheless an excess of synaptic refinement (enhanced pruning) has also been hypothesized to underlie the neuropathology of schizophrenia ([20]). Our results suggest that brain activity, in schizophrenia patients, is characterized by a subtle change of the global functional architecture, which is not totally random, but involves both an increase and a decrease of the local connectivity strengths. This probably follow from the attempt of the brain to compensate for an imbalance in local homeostatic signalling, that may in part rise from immune/inflammatory, oxidative stress, endocrine and metabolic cascades ([78]). Such untargeted compensation may homogenize the patterns of information spread in the brain, which is expected to reach all areas without the involvement of the whole system in activity ([79]). The alteration of weak and strong links distribution induces a lack of activity depression, which has to tend to confine the functional response to the modular size, leading, de facto, to a distributed and progressive crumbling of brain modularity.
Finally, it has been suggested that head motion may affect resting state functional MRI connectivity, especially in psychiatric patients. The subjects included in this study were selected to ensure comparable movement parameters, by including them only if they presented Framewise Displacement smaller than 0.5 mm ([80]). In summary, this study shows how previously reported fragmentation of the modular structure of functional connectivity in medicated schizophrenia patients is possibly due to a redistribution and consequent homogenization of the connectivity strengths between all the regions of the brain. Our findings support the theory that aberrant connectivity may induce deficits that propagate to higher cognitive functions through a bottom-up process ([72]). Moreover, we report the existence of several equivalent basal MSTs in patients, which implies the lack of specificity in the functional connectivity organization of the brain that is actually expected to be hierarchically set up in order to account the right integration for the right functioning.

Methods

Data acquisition and preprocessing

Forty four patients diagnosed with schizophrenia according to the DSM-V [9] criteria (SCZ group) were recruited. Other inclusion criteria were: 1) age between 18 and 65 years; 2) at least 8 years of education; 3) no dementia or cognitive deterioration according to the DSM-V, and a Mini-Mental State Examination score [10] higher than 24; and 4) suitability for a Magnetic Resonance Imaging (MRI) scan. Exclusion criteria were: 1) a history of alcohol or drug dependence or abuse in the last two years; 2) traumatic head injury, 3) any past or present major medical or neurological illness, 4) any other psychiatric disorder or mental retardation diagnosis and 5) MRI evidence of focal parenchymal abnormalities or cerebrovascular diseases. All patients were in a phase of stable clinical compensation and were receiving stable oral doses of one or more atypical antipsychotic drugs. Forty healthy controls were also recruited (HC group). They were rigorously matched for age, education and gender with the patients diagnosed as having schizophrenia. All HC were screened for any current or past diagnosis of DSM-IV axis I or II disorders. A diagnosis of schizophrenia or any other mental disorder in first-degree relatives was also an exclusion criterion.

A gradient-echo echo-planar imaging at 3T (Philips Achieva) with a (T2*)-weighted imaging sequence for the registration of the blood oxygen level-dependent (BOLD) signal (TR = 3 s, TE = 30 ms, matrix = 80 x 80, FOV=224x224, slice thickness = 3 mm, flip angle = 90°, 50 slices, 240 vol) has been used to collect fMRI data. We used a thirty-two channel receive-only head coil and we also acquire high-resolution T1-weighted whole-brain structural scans (1x1x1 mm voxels). Subjects were asked to keep their eyes open and their cardiac and respiratory cycles were also taken into account using respectively the scanner’s built-in photoplethysmograph and a pneumatic chest belt.

We applied an AAL mask [81] to parcellate the human brain in 116 anatomical regions. We extracted the fMRI signals at voxel level, then we averaged them in each region of interest ending up with 116 BOLD time-series. We, then, computed their pairwise similarity using the Pearson’s correlation coefficient obtaining a symmetric fully correlation matrix.

For each subject and each time-series, we removed possible sources of physiological variance: time-lock cardiac and respiratory artifacts by means of linear regression [82] (i.e., two cardiac and respiratory harmonics, respectively together with four interaction terms). We also looked for the effect of low-frequency respiratory and heart rates [83, 84, 85].

The pre-processing of fMRI data consisted in: head-motion and slice timing corrections plus the discard of voxels not belonging to brain (with FSL: FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl)

We used head motion parameters estimation to obtain the Framewise Displacement (FD). Time points with high FD (FD > 0.2 mm) were replaced using a least-squares spectral decomposition
following [80]. Then, we detrended, demeaned and band-pass filtered (frequency range 0.01-0.1 Hz) data using custom Matlab algorithms. We performed a 2-step registration in line with group-analysis: we first transformed fMRI data from functional space to the structural space of the subject with FLIRT (FMRIB’s Linear Registration Tool), then using Advanced Normalization Tools (ANTS: Penn Image Computing & Science Lab, [http://www.picsl.upenn.edu/ANTS/]) the data were non-linearly sent to a standard space (Montreal Neurological Institute MNI152 standard map). To conclude, we apply a spatial smooth to the final data (5x5x5 mm full-width half-maximum Gaussian kernel).

**Percolation Analysis and Thresholding**

For each subject separately, we ranked in increasing order the edge weights and removed from the related human functional brain network all of them one a time (for more details, see [46]). Then, at each step we counted the number of connected components forming the actual percolated network. At the end we reported on the y-axes of a graph the average number of connected components computed respectively over all healthy subjects (blue curve in fig 2(a)) and schizophrenic patients (red curve in fig 2(a) together with its 95% confidence interval and in correspondence of the specific correlation threshold on the x-axis. We also reported in fig 2 (b)-(c), the size of the giant component for each subject and each percolate network.

**Maximum Spanning Forest and Maximum Spanning Tree**

For each individual human functional brain network, we computed its Maximum Spanning Tree keeping for each node its strongest link and discarding all the others, and then connecting the resulting network components with only one connection: the strongest one not forming cycles (for more details, see [46]).

**Allometric Scale**

Once we have compute for each individual the MST of his human functional brain network, we considered all its possible directed versions obtained considering one at a time a different node as root and associating to the MST the induced direction. This means that we build 116 MSTs associated to the same subject. Such MSTs have exactly the same list of edges and weights, but differ for the directions of such links. Indeed, we introduced the directionality only after having compute the MST. This procedure avoids to make any arbitrary choice for the tree root. For each node in the MST, we computed two quantities: (i) $A_i$, the number of nodes forming the subtree having node $i$ as root (including $i$); and (ii) $C_i = \sum_k A_k$, where $k$ runs over all nodes in the subtree having root $i$ (including $i$). The shape of $C_i$ as a function of $A_i$ exhibits a clear power-low distribution: $C \propto A^\eta$.

**References**

1. Bassett, D. S. & Siebenhühner, F. Multiscale network organization in the human brain. *Multiscale Analysis and Nonlinear Dynamics* 179–204 (2013).
2. Bassett, D. S. & Sporns, O. Network neuroscience. *Nature neuroscience* 20, 353 (2017).
3. Braun, U. *et al.* From maps to multi-dimensional network mechanisms of mental disorders. *Neuron* 97, 14–31 (2018).
4. Camchong, J., MacDonald III, A. W., Bell, C., Mueller, B. A. & Lim, K. O. Altered functional and anatomical connectivity in schizophrenia. *Schizophrenia bulletin* 37, 640–650 (2009).
5. Cheng, W. et al. Voxel-based, brain-wide association study of aberrant functional connectivity in schizophrenia implicates thalamocortical circuitry. npj Schizophrenia 1, 15016 (2015).

6. Guo, S., Kendrick, K. M., Yu, R., Wang, H.-L. S. & Feng, J. Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. Human brain mapping 35, 123–139 (2014).

7. Bassett, D. S., Nelson, B. G., Mueller, B. A., Camchong, J. & Lim, K. O. Altered resting state complexity in schizophrenia. Neuroimage 59, 2196–2207 (2012).

8. Bassett, D. S. et al. Hierarchical organization of human cortical networks in health and schizophrenia. Journal of Neuroscience 28, 9239–9248 (2008).

9. Doucet, G. E., Bassett, D. S., Yao, N., Glahn, D. C. & Frangou, S. The role of intrinsic brain functional connectivity in vulnerability and resilience to bipolar disorder. American Journal of Psychiatry 174, 1214–1222 (2017).

10. Martino, M. et al. Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. Proceedings of the National Academy of Sciences 113, 4824–4829 (2016).

11. Castellanos, F. X. & Proal, E. Large-scale brain systems in adhd: beyond the prefrontal–striatal model. Trends in cognitive sciences 16, 17–26 (2012).

12. Mill, B. D. et al. Adhd and attentional control: Impaired segregation of task positive and task negative brain networks. Network Neuroscience 1–18 (2017).

13. Weinberger, D. R., Berman, K. F. & Illowsky, B. P. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: iii. a new cohort and evidence for a monoaminergic mechanism. Archives of general psychiatry 45, 609–615 (1988).

14. Stephan, K. E., Friston, K. J. & Frith, C. D. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophrenia bulletin 35, 509–527 (2009).

15. Singer, W. Neuronal synchrony: a versatile code for the definition of relations? Neuron 24, 49–65 (1999).

16. Varela, F., Lachaux, J.-P., Rodriguez, E. & Martinerie, J. The brainweb: phase synchronization and large-scale integration. Nature reviews neuroscience 2, 229 (2001).

17. Gregoriou, G. G., Gotts, S. J., Zhou, H. & Desimone, R. Long-range neural coupling through synchronization with attention. Progress in brain research 176, 35–45 (2009).

18. Singer, W. Distributed processing and temporal codes in neuronal networks. Cognitive neurodynamics 3, 189–196 (2009).

19. Fries, P. Rhythms for cognition: communication through coherence. Neuron 88, 220–235 (2015).

20. Boksa, P. Abnormal synaptic pruning in schizophrenia: Urban myth or reality? Journal of psychiatry & neuroscience: JPN 37, 75 (2012).

21. Stoneham, E. T., Sanders, E. M., Sanyal, M. & Dumas, T. C. Rules of engagement: factors that regulate activity-dependent synaptic plasticity during neural network development. The Biological Bulletin 219, 81–99 (2010).
22. Paolicelli, R. C. et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* 1202529 (2011).

23. Faludi, G. & Mirnics, K. Synaptic changes in the brain of subjects with schizophrenia. *International Journal of Developmental Neuroscience* 29, 305–309 (2011).

24. Biswal, B. B. et al. Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences* 107, 4734–4739 (2010).

25. Fox, M. D., Snyder, A. Z., Vincent, J. L. & Raichle, M. E. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron* 56, 171–184 (2007).

26. Meyer-Lindenberg, A. et al. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *American Journal of Psychiatry* 158, 1809–1817 (2001).

27. Meyer-Lindenberg, A. S. et al. Regionally specific disturbance of dorsolateral prefrontal–hippocampal functional connectivity in schizophrenia. *Archives of general psychiatry* 62, 379–386 (2005).

28. Esslinger, C. et al. Neural mechanisms of a genome-wide supported psychosis variant. *Science* 324, 605–605 (2009).

29. Lynall, M.-E. et al. Functional connectivity and brain networks in schizophrenia. *Journal of Neuroscience* 30, 9477–9487 (2010).

30. Skudlarski, P. et al. Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. *Biological psychiatry* 68, 61–69 (2010).

31. Fitzsimmons, J., Kubicki, M. & Shenton, M. E. Review of functional and anatomical brain connectivity findings in schizophrenia. *Current opinion in psychiatry* 26, 172–187 (2013).

32. Venkataraman, A., Whitford, T. J., Westin, C.-F., Golland, P. & Kubicki, M. Whole brain resting state functional connectivity abnormalities in schizophrenia. *Schizophrenia research* 139, 7–12 (2012).

33. Rashid, B. et al. Classification of schizophrenia and bipolar patients using static and dynamic resting-state fmri brain connectivity. *Neuroimage* 134, 645–657 (2016).

34. Sheffield, J. M. & Barch, D. M. Cognition and resting-state functional connectivity in schizophrenia. *Neuroscience & Biobehavioral Reviews* 61, 108–120 (2016).

35. Lewandowski, K. E. et al. Functional connectivity in distinct cognitive subtypes in psychosis. *Schizophrenia research* (2018).

36. Cole, M. W., Anticevic, A., Repovs, G. & Barch, D. Variable global dysconnectivity and individual differences in schizophrenia. *Biological psychiatry* 70, 43–50 (2011).

37. Bullmore, E. & Sporns, O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience* 10, 186–198 (2009).

38. Bollobás, B. Random graphs. In *Modern graph theory*, 215–252 (Springer, 1998).

39. Bollobás, B. *Graph theory: an introductory course*, vol. 63 (Springer Science & Business Media, 2012).
40. Uhlhaas, P. J. Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia. *Current opinion in neurobiology* **23**, 283–290 (2013).

41. Uhlhaas, P. J. & Singer, W. Abnormal neural oscillations and synchrony in schizophrenia. *Nature reviews neuroscience* **11**, 100 (2010).

42. van den Heuvel, M. P. *et al.* Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA psychiatry* **70**, 783–792 (2013).

43. Nelson, B. G., Bassett, D. S., Camchong, J., Bullmore, E. T. & Lim, K. O. Comparison of large-scale human brain functional and anatomical networks in schizophrenia. *NeuroImage: Clinical* **15**, 439–448 (2017).

44. Lerman-Sinkoff, D. B. & Barch, D. M. Network community structure alterations in adult schizophrenia: identification and localization of alterations. *NeuroImage: Clinical* **10**, 96–106 (2016).

45. Bordier, C., Nicolini, C., Forcellini, G. & Bifone, A. Disrupted modular organization of primary sensory brain areas in schizophrenia. *NeuroImage: Clinical* **18**, 682–693 (2018).

46. Mastrandrea, R. *et al.* Organization and hierarchy of the human functional brain network lead to a chain-like core. *arXiv preprint arXiv:1701.04782* (2017).

47. Duff, E. P., Makin, T., Cottaar, M., Smith, S. M. & Woolrich, M. W. Disambiguating brain functional connectivity. *Neuroimage* **173**, 540–550 (2018).

48. Gili, T. *et al.* The thalamus and brainstem act as key hubs in alterations of human brain network connectivity induced by mild propofol sedation. *The Journal of Neuroscience* **33**, 4024–4031 (2013).

49. Banavar, J. R., Maritan, A. & Rinaldo, A. Size and form in efficient transportation networks. *Nature* **399**, 130 (1999).

50. Garlaschelli, D., Caldarelli, G. & Pietronero, L. Universal scaling relations in food webs. *Nature* **423**, 165 (2003).

51. Ripke, S. *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421 (2014).

52. Shi, J. *et al.* Common variants on chromosome 6p22. 1 are associated with schizophrenia. *Nature* **460**, 753 (2009).

53. Consortium, I. S. *et al.* Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748 (2009).

54. Ripke, S. *et al.* Genome-wide association study identifies five new schizophrenia loci. *Nature genetics* **43**, 969 (2011).

55. Howson, J. M., Walker, N., Clayton, D., Todd, J. & Consortium, D. G. Confirmation of hla class ii independent type 1 diabetes associations in the major histocompatibility complex including hla-b and hla-a. *Diabetes, Obesity and Metabolism* **11**, 31–45 (2009).

56. Spalletta, G. *et al.* Glutathione s-transferase alpha 1 risk polymorphism and increased bilateral thalamus mean diffusivity in schizophrenia. *Psychiatry Research: Neuroimaging* **203**, 180–183 (2012).
57. Rose, E. J. et al. Effects of a novel schizophrenia risk variant rs7914558 at cmmn2 on brain structure and attributional style. The British Journal of Psychiatry 204, 115–121 (2014).

58. Fornito, A., Zalesky, A., Pantelis, C. & Bullmore, E. T. Schizophrenia, neuroimaging and connectomics. Neuroimage 62, 2296–2314 (2012).

59. Wheeler, A. L. & Voineskos, A. N. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Frontiers in human neuroscience 8, 653 (2014).

60. Fornito, A. & Bullmore, E. T. Connectomics: a new paradigm for understanding brain disease. European Neuropsychopharmacology 25, 733–748 (2015).

61. Cao, H., Dixson, L., Meyer-Lindenberg, A. & Tost, H. Functional connectivity measures as schizophrenia intermediate phenotypes: advances, limitations, and future directions. Current opinion in neurobiology 36, 7–14 (2016).

62. Calhoun, V. Data-driven approaches for identifying links between brain structure and function in health and disease. Dialogues in Clinical Neuroscience 20, 87 (2018).

63. Bardella, G., Bifone, A., Gabrielli, A., Gozzi, A. & Squartini, T. Hierarchical organization of functional connectivity in the mouse brain: a complex network approach. Scientific Reports 6, 32060 EP – (2016).

64. Gallos, L. K., Makse, H. A. & Sigman, M. A small world of weak ties provides optimal global integration of self-similar modules in functional brain networks. Proceedings of the National Academy of Sciences 109, 2825–2830 (2012).

65. Whitfield-Gabrieli, S. et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proceedings of the National Academy of Sciences pnas–0809141106 (2009).

66. Zhuo, C. et al. Functional connectivity density alterations in schizophrenia. Frontiers in behavioral neuroscience 8, 404 (2014).

67. Rashid, B., Damaraju, E., Pearlson, G. D. & Calhoun, V. D. Dynamic connectivity states estimated from resting fmri identify differences among schizophrenia, bipolar disorder, and healthy control subjects. Frontiers in human neuroscience 8, 897 (2014).

68. Fries, P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends in cognitive sciences 9, 474–480 (2005).

69. Akam, T. & Kullmann, D. M. Oscillations and filtering networks support flexible routing of information. Neuron 67, 308–320 (2010).

70. Van Dijk, K. R. & Drzezga, A. The default network of the brain. In PET and SPECT in Neurology, 169–181 (Springer, 2014).

71. Tomasi, D., Wang, G.-J. & Volkow, N. D. Energetic cost of brain functional connectivity. Proceedings of the National Academy of Sciences 110, 13642–13647 (2013).

72. Friston, K. J. The disconnection hypothesis. Schizophrenia research 30, 115–125 (1998).

73. Friston, K. Hierarchical models in the brain. PLoS computational biology 4, e1000211 (2008).
74. Bastos, A. M. et al. Canonical microcircuits for predictive coding. *Neuron* **76**, 695–711 (2012).

75. Clark, A. Whatever next? predictive brains, situated agents, and the future of cognitive science. *Behavioral and brain sciences* **36**, 181–204 (2013).

76. Cabral, J. et al. Structural connectivity in schizophrenia and its impact on the dynamics of spontaneous functional networks. *Chaos: An Interdisciplinary Journal of Nonlinear Science* **23**, 046111 (2013).

77. Tomasi, D. & Volkow, N. D. Mapping small-world properties through development in the human brain: disruption in schizophrenia. *PloS one* **9**, e96176 (2014).

78. Landek-Salgado, M. A., Faust, T. E. & Sawa, A. Molecular substrates of schizophrenia: homeostatic signaling to connectivity. *Molecular psychiatry* **21**, 10 (2016).

79. Russo, R., Herrmann, H. J. & de Arcangelis, L. Brain modularity controls the critical behavior of spontaneous activity. *Scientific reports* **4**, 4312 (2014).

80. Power, J. D. et al. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* **84**, 320–341 (2014).

81. Tzourio-Mazoyer, N. et al. Automated anatomical labeling of activations in spm using a macroscopic anatomical parcellation of the mni mri single-subject brain. *Neuroimage* **15**, 273–289 (2002).

82. Glover, G. H., Li, T.-Q. & Ress, D. Image-based method for retrospective correction of physiological motion effects in fMRI: Retroicor. *Magnetic resonance in medicine* **44**, 162–167 (2000).

83. Birn, R. M., Diamond, J. B., Smith, M. A. & Bandettini, P. A. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage* **31**, 1536–1548 (2006).

84. Shmueli, K. et al. Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI bold signal. *Neuroimage* **38**, 306–320 (2007).

85. Chang, C. & Glover, G. H. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *Neuroimage* **47**, 1448–1459 (2009).
Figure 8: **Allometric scale comparison for several MSTs** Exponent of the power law relation between the quantities $A_i$ and $C_i$ computed for different ranks of the MST and each subject separately. The second rank MST is obtained as the maximum spanning tree of the fully functional brain network once the first rank MST was removed from it and reported in (a); in the same way we obtained the allometric scale for the (b) third rank and the (c) fourth one. The quantity has been computed on the MST of each healthy subject and Schizophrenic patient separately changing the ROI chosen as root. Then, we reported the average allometric scale for the two groups together with their 95% confidence interval.