Research Paper

Functional Connectivity Alterations of Within and Between Networks in Schizophrenia: A Retrospective Study

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Citation Keyvanfard, F., Schmid, A., & Nasiraei-Moghaddam, A. (2023). Functional Connectivity Alterations of Within and Between Networks in Schizophrenia: A Retrospective Study. *Basic and Clinical Neuroscience, 14*(3), 397-410. http://dx.doi.org/10.32598/bcn.2022.3928.2

doi http://dx.doi.org/10.32598/bcn.2022.3928.2

Article info:
Received: 10 Jan 2022
First Revision: 27 Mar 2022
Accepted: 22 May 2022
Available Online: 01 May 2023

Keywords:
Schizophrenia, Cognitive dysfunction, fMRI, Resting state networks, Inter-network connectivity

ABSTRACT

Introduction: Schizophrenia (SZ) is a chronic brain disorder characterized by diverse cognitive dysfunctions due to abnormal brain connectivity. Evaluating these connectivity alterations between and within such networks (intra- and inter-connectivity) may improve the understanding of disrupted information processing patterns in SZ patients.

Methods: Resting-state fMRI analysis was performed on 24 SZ patients and 27 matched healthy controls. A functional connectivity matrix was constructed for each participant based on 129 gray matter regions. All regions were classified into eight distinct functional networks. Afterward, all functional connections were segregated into inter- and intra-network connections considering the eight networks. The Mean values of connectivity weights and nodal strength were examined for within- and between-network connections in SZ patients and healthy controls.

Results: This analysis revealed that the within-network connections in the somatomotor (SM) network significantly reduced ($P<0.001$) in SZ patients. Additionally, intra-network connections within the visual and the ventral attention (VA) networks were significantly lower ($P<0.01$) in the SZ group. Moreover, disrupted intra-network connectivity was detected between the following network pairs: The visual-limbic, the somatomotor-limbic, the dorsal attention-limbic, and the ventral attention-dorsal attention system.

Conclusion: The results showed an extensive reduction in functional connectivity strength for SZ patients, with a particularly significant decrease in intra-network connections when compared to the inter-networks. These findings can impact the understanding of the important dysregulated connections that are implicated in the incidence of schizophrenia.

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Highlights

- Intra-network connections are more altered in schizophrenia (SZ) compared to inter-network.
- The visual, somatomotor (SM), and ventral attention (VA) networks are more affected in SZ.
- The interactions between the limbic system and three resting-state networks (RSNs) are altered significantly.
- The nodal strengths in different regions of RSNs are reduced significantly in SZ.

Plain Language Summary

Brain functional connectivity is altered in several brain disorders. Looking for these changes may help in better understanding the disorder effects, its diagnostic and treatment. Our brain can be organized into distinct functional modules, known as resting-state networks (RSNs). These RSNs include visual, somatomotor (SM), fronto-parietal, dorsal attention, ventral attention, default mode (DMN), and limbic functional systems. In this study, we examined the alteration of functional connectivity in schizophrenia disorder considering these brain RSNs. The functional connections were classified in two groups, the inter- and intra-network connections. Inter-network connections are defined as the links between pairs of regions from two different brain subnetworks, whereas intra- network connections are determined as the connections between pairs of regions inside each network. Our analysis indicated that the functional connectivity strengths of intra-network connections reduced more in schizophrenia. It was also found that the connection between the limbic network and others is more disrupted compared to other inter-network links. These findings can help us in better understanding the effect of schizophrenia on the brain and therefore its treatment.

1. Introduction

Schizophrenia (SZ) is a mental disorder affecting approximately 1% of the world's population. It is primarily associated with dopamine dysfunction (Stahl, 2018; Yang & Tsai, 2017) and is characterized by diverse clinical features such as the disintegration of emotional responsiveness and thought processes. The emergence of SZ is a result of alterations in interactions between two or more brain regions, not regionally isolated pathologies (Andreasen et al., 1998; Friston & Frith, 1995; Stephan et al., 2009; Van Den Heuvel & Fornito, 2014). The findings of previous brain functional (Correa et al., 2009; Lawrie et al., 2002, Lawrie et al., 2008; Liu et al., 2009; Manoach et al., 2000) and structural studies (Dietsche et al., 2017; Karlsgodt et al., 2010; Lawrie et al., 2008; Stephen et al., 2013) have established that a considerable part of brain regions are involved in this disorder.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a popular analyzing method for functional connectivity (FC) assessment in brain networks. The rs-fMRI method is based on the temporally correlated blood oxygen level-dependent (BOLD) signals between distinct brain regions; thereby, FC analysis in a resting state condition can detect the coherent spontaneous neuronal activity within brain networks (Dietsche et al., 2017). Many studies have employed a seed-based approach in which a prior hypothesis about a varied region of interest (ROI) in SZ was used. However, it is also common practice to identify the alterations of a functionally connected brain at a "whole-brain" level in different disorders.

Several SZ studies have examined the relationship strength between pairs of brain regions across the entire brain (Fornito et al., 2012; Karbasforoushan & Woodward, 2013; Lynall et al., 2010). Furthermore, network characteristics have been widely investigated by many researchers with the graph theory method (Cabral et al., 2012; Karbasforoushan & Woodward, 2013; Liu et al., 2008; Lynall et al., 2010; Micheloyannis, 2012). Overall, findings of previous studies supported the existence of functional dysconnectivity in SZ patients

through the decrease of FC strength (Fornito et al., 2012; Skåtun et al., 2017; Skudlarski et al., 2010; Tu et al., 2013; Wei et al., 2018) and a reduction in other network measurements such as the clustering coefficient and efficiency (Algunaid et al., 2018; He et al., 2012; Karbasforoushan & Woodward, 2013; Liu et al., 2008; Rubinov & Bullmore, 2013; Yu et al., 2011).

On the other hand, the complex brain network can be considered as several modulated (sub)networks that are functionally linked brain regions sharing specific roles and responsibilities (Keyvanfard et al., 2020; Sporns, 2013; Sporns & Betzel, 2016; van den Heuvel & Hulshoff Pol, 2010).

The within- and between connectivity of these networks change during brain development and in disorder progress (Chan et al., 2014; Sporns & Betzel, 2016). Therefore, the characterization of alterations of within- and between modules SZ is important and has attracted increasing attention in recent years. For instance, decreased FC between the frontoparietal network and the visual (VIS) networks was reported for SZ patients Wu et al., 2017. Other studies have reported mixed findings. An increased FC was found between the default mode (DMN) and the central executive networks (Manoliu et al., 2014), an increased FC between the sensory processing and the DMN network, (Tu et al., 2013), and a decrease in FC within the DMN network (Li et al., 2019) were detected in SZ patients. Moreover, prominent cortico-subcortical disconnections within the frontoparietal network (Tu et al., 2013) and disrupted connectivity among their nodes (Shinn et al., 2015) were demonstrated for SZ patients.

However, the reason for this discrepancy within and between established resting-state networks (RSNs) remains unclear due to mixed and different results (Hummer et al., 2020; Manoliu et al., 2014). Several studies have examined within and between-network connectivity

separately (Skåtun et al., 2017; Skudlarski et al., 2010) or focused on considering particular networks and not all RSNs (Mamah et al., 2013; Manoliu et al., 2014; Tu et al., 2013). In other words, their analysis was not performed comprehensively covering whole the brain.

This study aimed to understand how interactions inside RSNs or between them changed in SZ patients in comparison to healthy participants. Therefore, alterations in brain functional dysconnectivity between and within RSNs were examined in SZ patients and healthy controls (HC) along with a whole brain network analysis. Additionally, nodal strength variation was assessed to characterize an alteration pattern for inter-and intra-network comparison to the whole brain. It was hypothesized that the between-network connectivity is most affected by the SZ disorder.

2. Materials and Methods

Participants

Rs-fMRI analysis was performed in 27 SZ subjects (mean age, 41.9±9.6) and 27 age-matched healthy individuals (mean age, 35±6.8). The dataset is available on the Zenodo platform (Gutiérrez-Gómez et al., 2020; Vohryzek et al., 2020). The patients in the schizophrenic group were recruited from the Service of General Psychiatry at the Lausanne University Hospital. They met DSM-IV criteria for schizophrenic and schizoaffective disorders (American Psychiatry Association, 2000). Healthy control with major mood, psychotic, or substance-use disorders and having first-degree relatives with a psychotic disorder were excluded from this database. Moreover, a history of neurological disease was an exclusion criterion for all subjects (Gutiérrez-Gómez et al., 2020). The data analysis was further carried out in 24 out of 27 patients of the SZ group because only 24 subjects were under an equivalent medication dose of chlorpromazine (CPZ) (mean medication 431±288 mg) (Andreasen et al., 2010). Data of all subjects were fully anonymized.

Data acquisition and preparation

For each participant, a T1-weighted anatomical image and an rs-fMRI scan were acquired using a 3T Siemens Trio Scanner equipped with a 32-channel head coil. The magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence was applied for T1-weighted imaging with a resolution of 1×1×1.2 mm^3 and TI/TE/TR=900/2.98/2300 ms. Gray matter was partitioned into 129 cortical regions of interest (ROI) including 114 cortical ROIs, and 15 subcortical nuclei along with the brain stem, by employing the Desikan Killian atlas (Desikan et al., 2006). Each rs-fMRI scan covered a period of 8 minutes with a 3.3 mm voxel size (isotropic) and TE/TR=30/1920 ms. Data preprocessing included the exclusion of the first four time points of signals, regressing out of physiological signals (white-matter and cerebrospinal fluid), motion correction, spatial smoothing, and band-pass filtering, and a linear registration to the T1-weighted image was performed in the whole dataset. Finally, the functional matrices were obtained by computing the absolute value of the Pearson correlation between individual brain regions' time courses to extract the strength of the connections. Consequently, one connectivity matrix was generated with the K×K dimension (with K=129 numbers of brain regions) for each participant. Further details of the data acquisition and the preparation steps can be found in Vohryzek et al., 2020. This workflow is shown in Figure 1.

Data analysis and statistics

For the resting-state connectivity analysis of this study, a well-known RSNs map from Yeo, (Yeo et al., 2011) was adopted, which introduces seven functional subnetworks. In their parcellation, the cortex was divided into the VIS, SM, fronto-parietal (FP), dorsal attention (DA), ventral attention (VA), DMN, and limbic (limb) functional systems (Yeo et al., 2011). In addition to these seven cortical regions, there is one subnetwork that compromised all subcortical (non-cerebellar) parts of the brain. Subsequently, each brain region was allocated to one of these in total eight functional subnetworks.

The group difference analysis between the control and the SZ group was conducted in three steps. First, to compare the connectivity strengths between both groups, the mean weight for every connection was computed aside from the networks they belong to. Likewise, nodal strength was calculated with the brain connectivity toolbox (Rubinov & Sporns, 2010) and the values of the two groups were compared. In the second step, all connections were classified into two sets of inter- and intra-network connections. Inter-network connections are defined as the links between pairs of regions from two different networks, whereas intra- network connections are determined as the connections between pairs of regions inside each network. To understand the severity of changes in inter- and intra-network connections, the Mean values of these two connection sets were assessed between SZ patients and HC. As the third step, the inter- and intra-network connectivity of all eight brain networks was statistically compared between the control and patient groups. All statistical analyses involved a paired sample t-test. Bonferroni correction was used to correct for multiple comparisons. Finally, results with a $P<0.05$ were considered statistically significant. The entire analysis was performed using MATLAB software, version 2021a.

3. Results

Whole brain connectivity comparison

The statistical analysis of all connections in SZ patients compared to the ones in healthy individuals revealed a significant whole-brain difference for 1176 connections among 8256 edges (14.24%). For a clearer visual representation, the altered brain connectivity was mapped onto a cortical surface map. Figure 2a displays the regions including nodes with altered connections; accordingly, the different colors represent the normalized values in [0, 1]. The normalized value is determined by the nodal strength divided by the

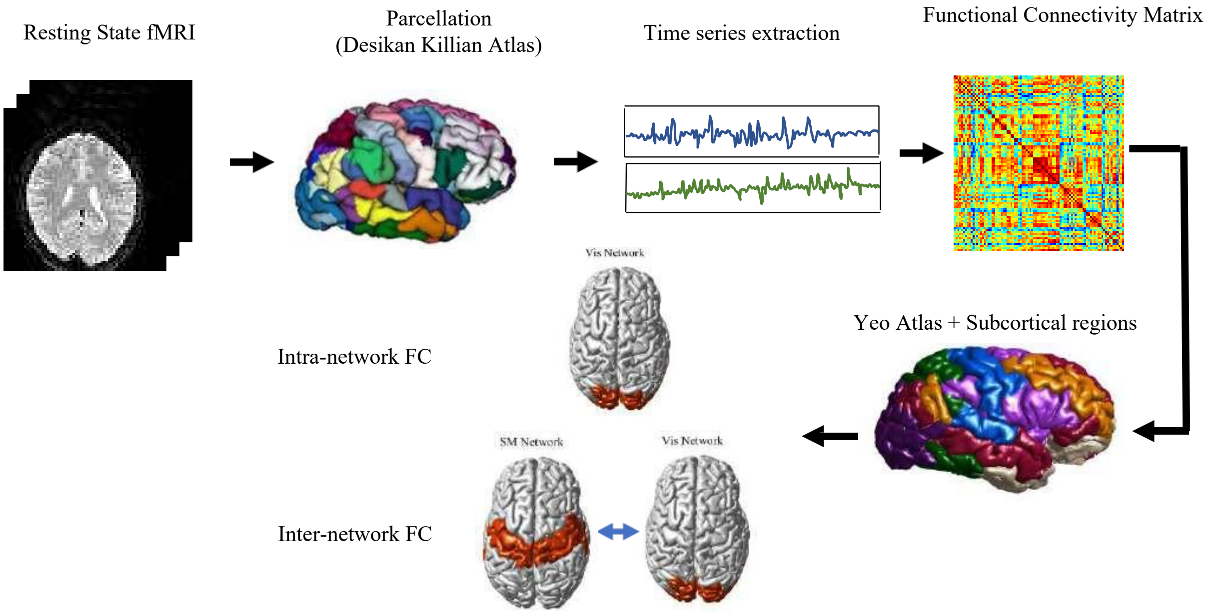

Figure 1. Flowchart of the method pipeline

Time series of 129 regions extracted from rs-fMRI and functional connectivity matrices were generated employing Desikan Killian atlas. Connections were divided into inter-and intra-network based on eight networks. The connectivity strength and nodal strength of inter- and intra- networks were assessed.

Table 1. Area name and abbreviations

Abbreviations	Region Name	Abbreviations	Region Name
LOF	Lateral orbitofrontal gyrus	SPaG	Superior parietal gyrus
pOrb	Pars orbitalis	IPaG	Inferior parietal gyrus
FP	Frontal pole	PCUN	Precuneus
MOF	Medial orbitofrontal gyrus	Cun	Cuneus
PTRI	Pars triangularis	PCAL	Pericalcarine cortex
POPE	Pars opercularis	LOCG	Lateral occipital gyrus
rosMFG	Middle frontal gyrus, rostral	LgG	Lingual gyrus
SFG	Superior frontal gyrus	FG	Fusiform gyrus
caMFG	Middle frontal gyrus, caudal	PHG	Para-hippocampal gyrus
PrG	Precentral gyrus	EC	Entorhinal cortex
PaG	Paracentral lobule	TP	Temporal pole
rosACG	Anterior cingulate gyrus, rostral	ITG	Inferior temporal gyrus
caACG	Anterior cingulate gyrus, caudal	MTG	Middle temporal gyrus
PcG	Posterior cingulate gyrus	bnkST	Bankssts
ICG	Isthmus cingulate gyrus	STG	Superior temporal sulcus
PoG	Postcentral gyrus	trTG	Transverse temporal gyrus
SMAR	Super marginal gyrus	Ins	Insula

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largest value of strength. More specifically, one of the compromised regions with several changed edges was related to a part of the SM network, which can be seen in red in Figure 2a.

Regarding the inter-and intra-network variations perspective, a higher percentage of intra-network edges (19.47%) seemed to be changed when compared to the inter-network (13.41%). The group comparison of the nodal strength was accomplished. It is commonly defined as the summation of all connection weights linked to the node. This comparison exhibited a significant difference in 37 nodes. As displayed in Figure 2b, the differences of the cortex nodal strength were observed in the bilateral precentral gyrus (PrG), posterior cingulate gyrus (PcG), superior frontal gyrus (STG), postcentral gyrus (PoG), paracentral lobule (PaG), super marginal gyrus (SMAR), superior parietal gyrus (SPaG), superior frontal gyrus (SFG), medial orbitofrontal gyrus (MOF), fusiform gyrus (FG), middle temporal gyrus (MTG), insula (Ins) and right temporal pole (TP), left lingual gyrus (LgG), and transverse temporal gyrus (trTG). These regions partly overlap with the map of the altered edges in Figure 2a. The abbreviations of all region names are listed in Table 1.

Intra- and inter-network comparisons

After the classification of all connections into inter-and intra-networks, a statistical analysis was applied for both connectivity groups, the SZ patients and the control subjects. A t-test was carried out from two different viewpoints. In the first approach, the weights for inter- and intra-networks were averaged for each subject of the two groups and therefore, two vectors with 27 and 24 elements (representing the number of participants in the healthy and SZ group) were obtained. The control group showed a significantly higher intra-network FC than the SZ groups. On the other hand, no significant difference was detected between the inter-network edges as shown in Figure 3. Furthermore, patients generally showed greater variance in both inter-and intra-network connections ($P<0.0001$) which illustrates greater diversity in functional connectivity in SZ patients (Bassett et al., 2012).

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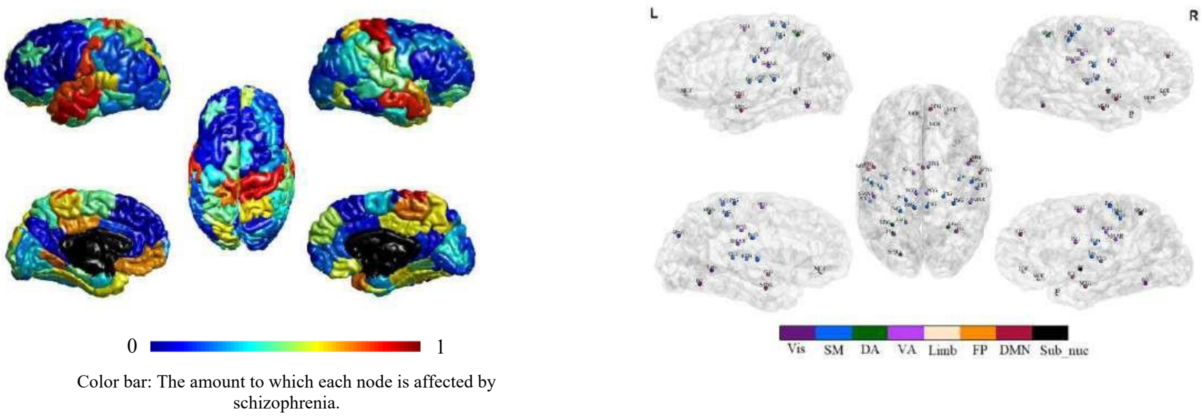

Figure 2. Altered regions of whole brain in SZ patients comparing to healthy individuals

a) Number of significantly altered edges connected to each node was counted and normalized into [0, 1]. The normalized value was coded on the brain surface map by color.

b) Significantly different nodal strength in patients is characterized by the color of networks to which they belong.

In the second comparison approach, a two-sampled t-test was applied on each inter-network connection as well as on the intra-network connection, which revealed a significant change in 955 out of 7121(13.41%) and 221 connections out of 1135(19.47%) for the inter-and intra-network respectively.

Intra-and inter-network comparisons of eight networks

Comparing the inter-and the intra-networks between healthy individuals and patients indicated that control subjects had higher connectivity weights within the RSNs (Figure 4a). However, this difference was significant for the visual, somatomotor (SM), and VA networks. The inter-network connectivity assessment revealed that connections between the limbic system and three networks including the visual, the SM, and the DA networks were disrupted in SZ. In addition, the connections between the DA and theVA networks were significantly weaker in the SZ group (Figure 4a-c). No other between-network differences appeared to be remarkably affected (Figure 4b).

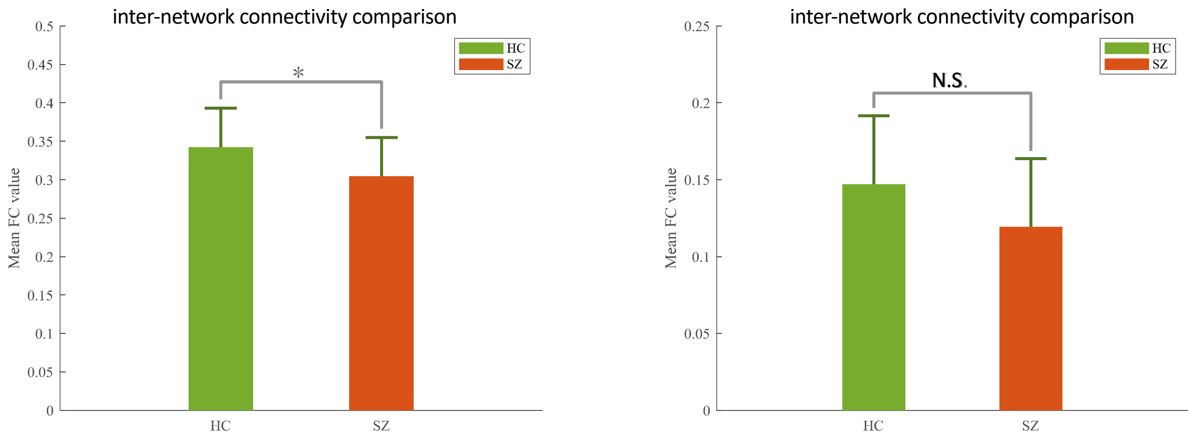

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Figure 3. Comparison of the intra-network connections (left) and the inter-network connections (right) between healthy controls and schizophrenia patients

Only intra-network connections indicated a significant difference between HC and SZ. N.S: Not significant, $^{*}P<0.05$).

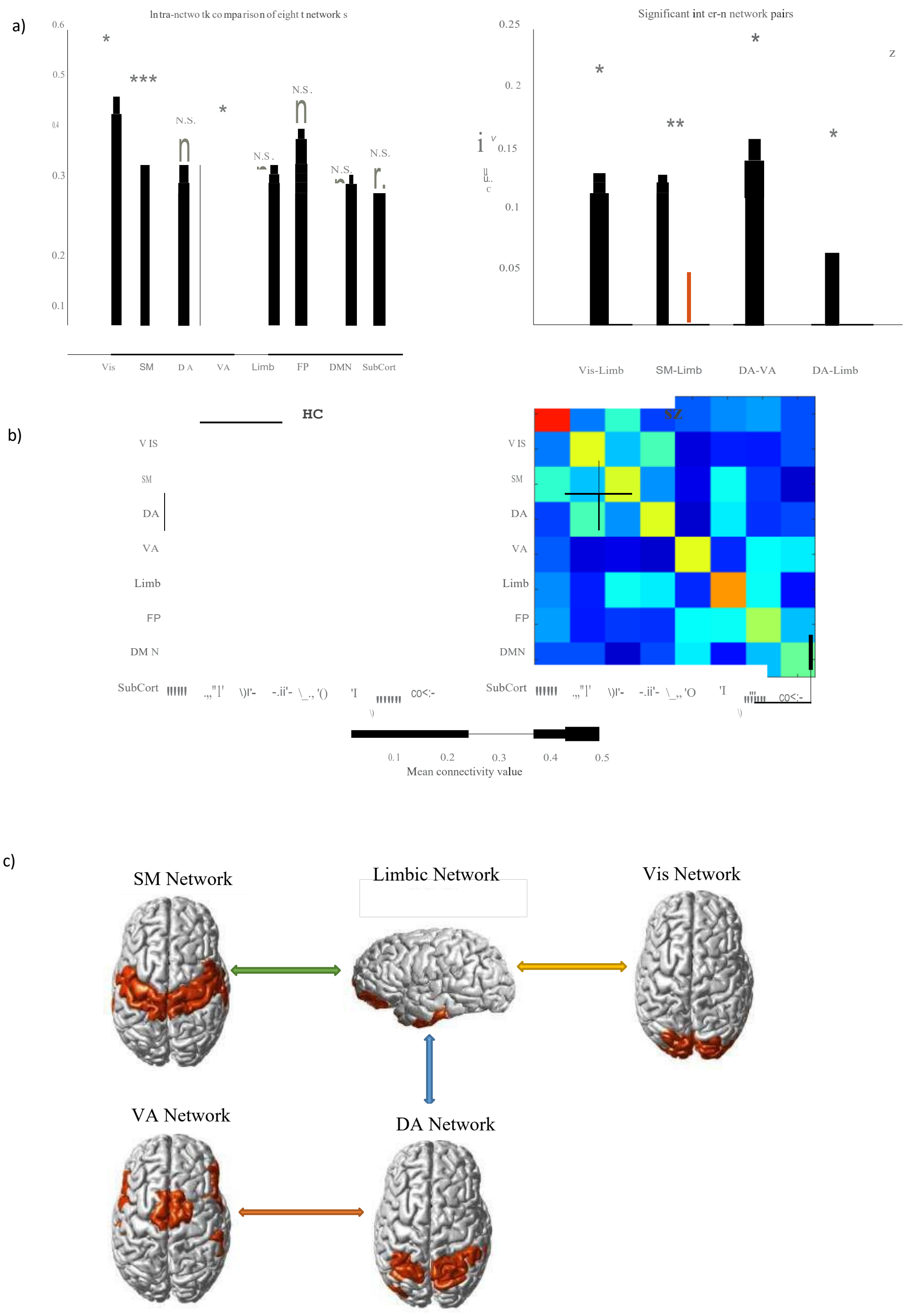

Figure 4. Modular comparison of functional connectivity in healthy control and SZ patients

a) Comparison of mean functional connectivity of inter- and intra-network through the bar graph.

b) Each element of control and patient matrices represents mean connectivity between all pairs of regions within or between networks.

c) Representation of the significant different inter-networks between HC and SZ.

NS: Not significant, *P<0.05, **P<0.01, ***P<0.001)

The affected nodal strength is illustrated in Figure 5 indicating that the networks demonstrated a reduced inter- and intra-network connectivity. As illustrated in Figure 5a, the affected nodal strength of intra-networks is concentrated in the SM network. Nodes that are involved in varying inter-network connectivity between the four mentioned networks are also shown in Figure 5b.

4. Discussion

In this study, we aimed to investigate to what extent schizophrenia disorder affects inter- and intra-network functional connections, as well as brain networks. Regarding the inter-and intra-network variations perspective, a higher percentage of intra-network edges (19.47%) seemed to be changed in comparison to inter-networks (13.41%). One possible explanation for this observation would be that some basic symptoms of SZ such as motor disturbances, impaired bodily sensations, and fatigue (Larson et al., 2010; Miret et al., 2016) can be related to within-network connection impairments.

The significant intra-network alterations are allocated to the visual, SM, and VA networks. Prior research has confirmed that visual impairments are one of the most important manifesting features in SZ (Kogata & Iidaka, 2018; Silverstein et al., 2015; van de Ven et al., 2017). Therefore, it can be assumed that the drastic impairment of the within-network connectivity in the visual system can compromise the vision of these patients. Moreover, slow movement or useless and excessive movement is another important symptom of SZ, which can be attributed to SM connectivity impairment (Adhikari et al., 2019; Kebets et al., 2019; Potvin et al., 2021; Shinn et al., 2015; Singh et al., 2014; Skåtun et al., 2017; Walther & Strik, 2012). The VA network is obtained as the third network experiencing intra-network alterations and it must be underlined that this network is closely related to the so-called "salience network." The salience network is proven to be implicated in the pathophysiology of schizophrenia and its dysfunction results in the incorrect assignment of salience. This can in turn lead to the key symptoms of schizophrenia including delusions

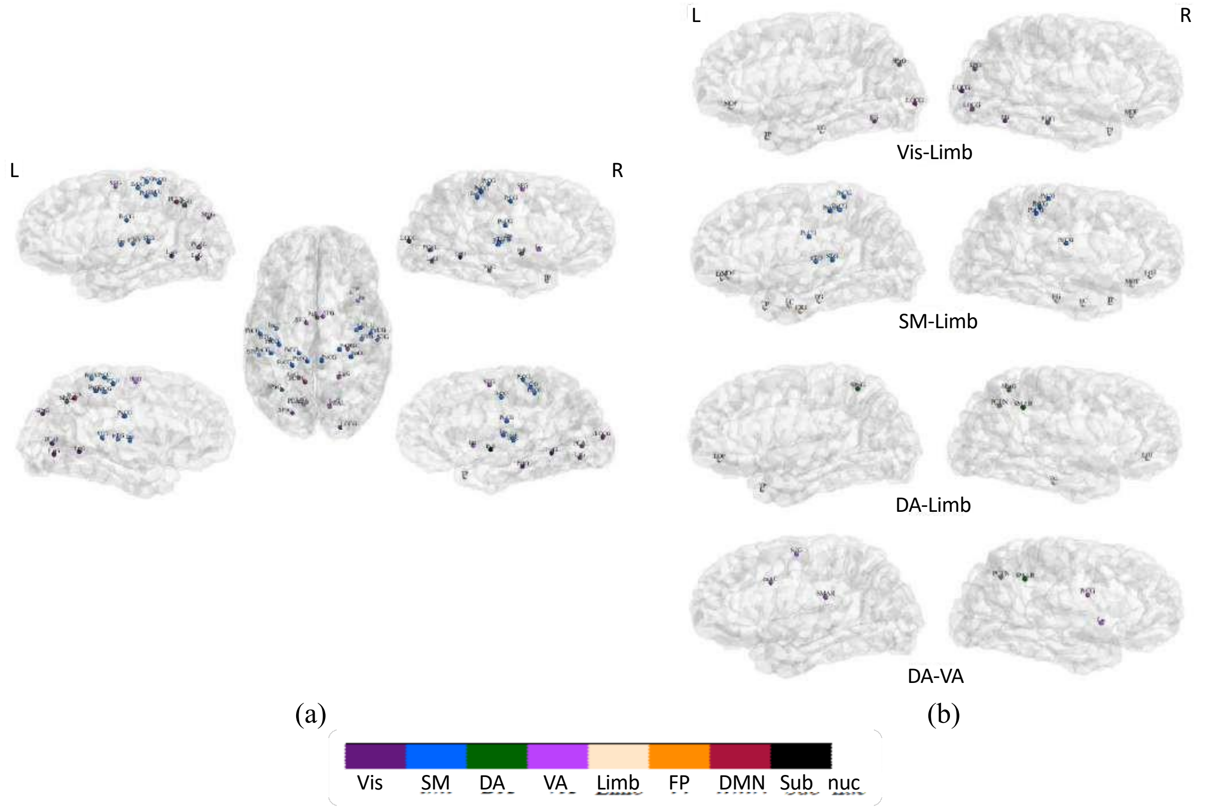

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Figure 5. Regions with reduced nodal strength. These altered nodes were obtianed by considering

a) Intra-network

b) Inter-network connectivity.

(Jimenez et al., 2016; Palaniyappan & Liddle, 2012; Smucny et al., 2016; Wynn et al., 2015).

Regarding inter-network connectivity, the patient group demonstrated lower connectivity between the four networks. Most notably, functional connections between the limbic system and three cortical networks were significantly affected in SZ patients. In line with this finding, several studies have reported impaired cortico-limbic functional connectivity in schizophrenia patients (Comte et al., 2018; Vai et al., 2015; Wang et al., 2021). Although the examination of between-network dysconnectivity in SZ is limited to a few studies, recent work has provided evidence for alterations in FC in between-networks for the visual-limbic (Cao et al., 2016), the somatomotor-limbic (Hummer et al., 2020), and the dorsal attention-limbic systems (Comte et al., 2018). Furthermore, a between-network dysconnectivity was found between the DA-VA network, which was previously reported to be impaired in SZ patients (Hummer et al., 2020).

Abnormal connectivity between functional networks indicated impaired communication between these networks. This abnormality is potentially harming the ability to connect separate psychological and neurobiological constructs into a cohesive whole necessary for daily functioning. The interaction of the limbic system with cortical networks supports a variety of functions including emotion processing and excitation/inhibition in behavior and memory, whereas abnormal expression and regulation of emotions and impairment in the memory and cognition of patients with SZ are confirmed (Guo et al., 2019; Gur & Gur, 2013; Tu et al., 2013; Zhang et al., 2019). Remarkably, connections inside the limbic system were not proven to be significantly different, and therefore, its interaction with other networks is assumed to have a stronger effect on the symptoms of these patients.

Contrary to our findings, several researchers have reported a notable alteration (reduction or increment) of DMN and FP connections in addition to other networks in SZ patients (Galindo et al., 2017; Guo et al., 2017; Whitfield-Gabrieli et al., 2009). In this study, reduced connectivity within and between networks failed to survive the significant threshold. One possible reason for this discrepancy could be distinct data analyzing procedures. Data (pre-) processing steps including the selection of brain regions and network definition may cause these differences. Here, a priori-defined network based on a well-known atlas was utilized for the analysis, as opposed to data-driven approaches (such as independent component analysis (ICA)). Certainly, network definition has an undeniable impact on the number of connections and Mean value of within- and between- networks. In this study, we defined nodes as distinct brain regions through automatic parcellation of each participant's brain via anatomical landmarks (FreeSurfer), as opposed to spatially uniform nodes (Baker et al., 2014) or performing a voxel-wise analysis (Gong et al., 2016).

In the assessment of the nodal strength, it is noteworthy that more significant changes occurred in the brain modular viewpoint. The strength of several nodes had not shown a remarkable difference in the whole brain evaluation (Error! Reference source not found [b]). In other words, the total number of altered nodes in a modular viewpoint is 58 nodes, which is 21 more than the number of nodes with reduced nodal strength throughout the whole brain. This suggests that some connections may compensate for the effect of other edges' weight reduction. However, further research is required to examine this hypothesis.

5. Conclusion

In conclusion, it was found that SZ has a stronger effect on within-network connectivity than on between-network connectivity. In a modular viewpoint of the intra-network assessment, the visual, SM, and VA regions demonstrated a significant reduction in the patient group. Furthermore, the main alterations of inter-networks were attributed to interactions between the limbic system and three other cortical networks which highlighted the importance of the limbic system implicated in daily life activities. In addition, a higher number of regions with reduced nodal strength were discovered through the network viewpoint. This may illustrate the brain's attempt to compensate for FC reductions and represents a topic of further research. Future studies could further investigate other graph-theoretic parameters such as e.g. the efficacy, and path length in each subnetwork.

Limitations

Some of the limitations of this study should be mentioned. In the current study, a dataset was used retrospectively, which included a rather low number of individuals. This may affect the precision of the obtained results. Therefore, a larger sample size is needed to confirm our findings in the future. Moreover, all subcortical regions were determined as one section while the cortex was parcellated into functionally defined regions. Consequently, a finer parcellation obtained with a higher image resolution might capture cortical-subcortical associations better.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization: Anna-Katharina Schmid and Abbas Nasiraei-Moghaddam; Methodology, investigation, formal analysis and writing original draft: Farzaneh Keyvanfard; Review and editing: Anna-Katharina Schmid and Farzaneh Keyvanfard; Supervision, and project administration: Abbas Nasiraei-Moghaddam; Fianl approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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