Hypoconnectivity networks in schizophrenia patients: a voxelwise meta-analysis of rs-fMRI

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Abstract

In the last few years, the field of brain connectivity has focused on identifying biomarkers to describe different health states and to discriminate between patients and healthy controls through the characterization of brain networks. A particularly interesting case, because of the symptoms' severity, is the work done with samples of patients diagnosed with schizophrenia. This meta-analysis aims to identify connectivity networks with different activation patterns between people diagnosed with schizophrenia and healthy controls. Therefore, we collected primary studies exploring whole brain connectivity by functional magnetic resonance imaging at rest in patients with schizophrenia compared to healthy people. Thus, we identified 25 high-quality studies that included a total of 1285 people with schizophrenia and 1279 healthy controls. The results indicate hypoactivation in the right precentral gyrus and in the left superior temporal gyrus of people with schizophrenia compared with the control group. These regions have been linked to deficits in gesticulation and the experience of auditory hallucinations in people with schizophrenia. A study of heterogeneity demonstrated that the effect size was influenced by the sample size and type of analysis. These results imply new contributions to the knowledge, diagnosis, and treatment of schizophrenia both clinically and in research.

Introduction

Schizophrenia is the most important severe mental health disorder and implies an extraordinary health problem. Risk factor identification and etiological studies remain unresolved in the scientific response. The genetic and neurobiological factors that have been associated with schizophrenia are quite heterogeneous. Several studies have focused on the dopaminergic dysfunction hypothesis concerning schizophrenia. For example, dopaminergic hypoactivity has been associated with the prefrontal cortex with negative symptomatology (Buckley and Castle, 2015). Currently, there is no biological marker for the diagnosis of schizophrenia. Thus, the early identification of people with a high risk of schizophrenia poses a major public health challenge before they begin to manifest the symptomatology of the disorder (Lewis, 2012). Consequently, a better understanding of this disorder's neurological substrates can help to identify better strategies for early diagnosis and psychological and individualized pharmacological treatment (Nickl-Jockschat and Abel, 2016).

Functional magnetic resonance imaging in the resting state (rs-fMRI) has proven to be a promising tool to contribute to the diagnosis of several disorders, such as autism (Anderson et al., 2011), attention and hyperactivity deficit disorder (Zhu et al., 2008), major depression disorder (Craddock, Holtzheimer, Hu and Mayberg, 2009) and schizophrenia (Chyzhyk and Graña, 2015; Chyzhyk, Savio and Graña, 2015; Rashid et al., 2016; Wang et al., 2018; Qureshi, Oh and Lee, 2019). Thus, it is a noninvasive technique and does not require the active collaboration of the patient (Lee, Smyser, and Shimony, 2013), which is especially important for evaluating brain activity in those populations that have affected their cognitive performance. In the study of connectivity in rest and schizophrenia, evidence has shown significant differences in patients compared to healthy populations. More specifically, the disconnection hypothesis has been studied, a framework in which the diversity of symptoms typical of schizophrenia is

conceptualized as a result of disconnections in neural networks (Friston and Frith, 1995). In line with this hypothesis, alterations in the default mode network (DMN), the most prominent resting network (Woodward, Rogers and Heckers, 2011), have been shown. In addition, a reduction in precuneus connectivity with other areas was noted in patients with schizophrenia compared to the control group. Connectivity intensity in this area is negatively correlated with the severity of negative symptoms, more specifically with the apathy domain (Forlim et al., 2020). Gangadin et al. (2021) also demonstrated a reduction in the connectivity of the hippocampal-mesencephal-striate network in patients with schizophrenia. In addition, patients showed increased long-range positive connectivity in the right middle frontal gyrus (MFG) and short-range positive connectivity in the right MFG and right superior medial prefrontal cortex, which are brain regions in the anterior DMN (Wang et al., 2018). Hua et al. (2018) noted decreased connectivity between the thalamus and prefrontal cortex and cerebellum but an increase in the connectivity of the thalamus and the motor cortex in patients with schizophrenia. In addition, studies of bilateral asymmetric connectivity have noted that patients with a predominance of positive symptomatology showed significantly more asymmetry to the left hemisphere. Instead, the predominance group of negative symptoms showed more asymmetry to the right. These results suggest that predominantly positive and predominantly negative schizophrenia may have different neural bases and that certain regions in the frontal and temporal lobes, as well as the gyrus and precuneus, play an essential role in mediating the symptoms of this disorder (Ke et al., 2009). Additionally, Chen et al. (2013) showed evidence that cerebellum disconnection is network-specific; that is, the group of patients with schizophrenia showed decreased cerebellum connectivity with the prefrontal lobe and more cortico-cerebellar connectivity with regions involved in sensory-motor processing, which may be indicative of the deficiencies in inhibition observed in people with schizophrenia. In addition, Li et al. (2019), also with schizophrenia patients, showed reduced insula connectivity with the sensory cortex and putamen compared to people with a high risk of psychotic disorder. Complementarily, schizophrenia patients have shown increased connectivity between the posterior cingulate cortex and the inferior left gyrus, mid-left frontal gyrus, and mid-left temporal gyrus. Conversely, schizophrenia patients have shown decreased connectivity in the executive control network and the dorsal attention network. These results show that resting-state network connectivity is altered in patients with schizophrenia, so the alterations are characterized by reduced segregation between the DMN and the executive control networks in the prefrontal cortex and temporal lobe (Woodward, Rogers and Heckers, 2011). This study found no statistically significant distinctions in the connectivity of the salience network; instead, Huang et al. (2019) showed evidence of hyperconnectivity of the salience network and the prefrontal cortex and cerebellum, as well as hypoconnectivity between the cortico-striatal-thalamic-cortical subcircuit and the salience network.

In recent years, some meta-analyses have explored rs-fMRI in patients with schizophrenia compared to control groups. For example, Xiao et al. (2017) showed evidence that people with schizophrenia had increased connectivity, estimated with regional homogeneity (ReHo), in the right superior frontal and right superior temporal gyrus, as well as decreased ReHo connectivity in the right fusiform gyrus, left superior temporal gyrus, left postcentral gyrus, and right precentral gyrus (focused on ReHo

studies). Dong et al. (2018) conducted a meta-analysis showing that patients with schizophrenia presented hypoconnectivity in the DMN, affective network (AN), ventral attentional network (VAN), thalamic network (TN), and somatosensory network. They also showed hypoconnectivity between VAN and TN, VAN and DMN, VAN and the frontoparietal (FN), between FN and TN, and between FN and DMN. Only hyperconnectivity was found between the AN and VAN (focused on seed-based analysis studies). The abovementioned Li et al. (2019) showed evidence through a meta-analysis that supports hypoconnectivity in certain brain networks in schizophrenic patients. More specifically, the self-referential network (superior temporal gyrus) and DMN (right medial prefrontal cortex and left precuneus and anterior cingulate) focused on independent component analysis (ICA) studies. Finally, Gong et al. (2020) showed that people with schizophrenia presented a decreased amplitude of low frequencies (ALFF) in the bilateral postcentral gyrus, bilateral precuneus, left inferior parietal gyrus, and right occipital lobe. In addition, they found an increased ALFF in the right-handed, left inferior frontal gyrus, left inferior temporal gyrus, and right anterior cingulate cortex.

To our knowledge, no meta-analysis includes rs-fMRI studies involving the whole brain, as well as studies that use different analysis techniques (ICA, ReHo, ALFF, fALFF, etc.). Moreover, given the incongruences between the studies in this field, the aim of this meta-analysis is to identify functional connectivity networks of the whole brain using a paradigm of rs-fMRI in patients with schizophrenia compared to healthy people (without any neurological or psychiatric disorder). Thus, it is expected that patients diagnosed with schizophrenia will show statistically significant differences in functional connectivity compared to healthy people. In addition, a secondary objective is to analyze the relationship between the effect size and mediator variables, such as sample size, age, gender, etc.

Methods

Study selection. Two independent investigators performed a bibliographic search using the following databases: PubMed, Web of Science (WoS), Psycinfo, Google Scholar, and Scopus. Additionally, the Boolean algorithm with the keywords used is presented in Supplementary Appendix 1. We included studies published until February 28, 2021. This meta-analysis was conducted according to the “Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)” guidelines. The inclusion criteria for the studies were as follows: 1) they were published in English or Spanish; 2) the full text was available; 3) they were a primary study in a human population; 4) they included a patient group diagnosed with schizophrenia following the DSM-IV criteria or the structured clinical interview for DSM-IV (SCID); 5) they compared brain activation between schizophrenia patients and healthy people; 6) they used rs-fMRI; or 7) the studies reported Montreal Neurological Institute (MNI) or Talairach coordinates of the whole brain contrast comparing schizophrenia persons and control subjects. The exclusion criteria were as follows: 1) systematic reviews or meta-analysis; 2) methodologic studies; 3) patients with schizophrenia with other psychiatric or neurological disorders; or 4) studies focused on dynamic connectivity or use graph analysis or any other technique that does not identify coordinates. The studies were screened out as shown in Figure 1. Our search yielded a total of 3563 studies [WoS ($n = 1123$), Scopus ($n = 823$), PubMed ($n = 729$), PsycInfo ($n = 543$), and Google Scholar ($n = 345$)]. Subsequently,

2106 duplicate papers were removed through Mendeley, and 64 duplicate papers were removed via Rayyan. A total of 1234 studies were excluded after title/abstract screening because they did not meet the inclusion criteria. Later, 159 articles were sought to read the full text, but 8 studies could not be found. Thus, after the full-text screening, 73 studies were excluded because they did not provide information about the peak activation coordinates, 16 because they did not report on the statistics associated with the coordinates, and 37 because they did not analyze the whole brain. Finally, only 25 studies matching our inclusion criteria were included and are marked with an * in the reference list. In addition, we obtained a 100% rate of agreement between the two investigators for the study search and selection.

Voxel-Wise Meta-analysis. We used seed-based d mapping (SDM) software (available at <http://www.sdmproject.com>) to analyze the differences between schizophrenia patients and healthy subjects. The approach details have been described in Radua and Mataix (2012) or Müller et al. (2018). First, the reported peak coordinates of all functional differences, which were statistically significant at the whole brain level in these studies, were chosen. We ensured that all included studies used the same statistical threshold throughout the whole brain to avoid possible bias toward regions with liberal thresholds. Thus, we considered the minimum threshold to be defined by a .001 significance value and Student's t reference value with the degrees of freedom of each study estimated by the conventional expression (n_1+n_2-2) . Second, we recreated peak coordinates for each study with a standard MNI map of the group difference effect size based on their peak t value by means of a nonnormalized Gaussian kernel to the voxels near the peak, which assigns higher values to the voxels closer to peaks. Third, the mean map was obtained by voxelwise calculation of the study map random-effects mean, weighted by the sample size. Fourth, to correctly balance the sensitivity and specificity, we used the p value of 0.05 as the main threshold with an additional peak height of $z = 1$. Jackknife sensitivity analysis was performed to test the replicability of the results. After the calculation of Cohen's d and the confidence interval (CI) analysis of the different papers was performed, a descriptive analysis of every paper result was resumed in different images to clarify the results obtained in every included study.

Quality Assessment. We assessed the quality of the included studies using a checklist consisting of 11 items that focused on the clinical characteristics of the participants, the neuroimaging and data analysis methodology, the results, and the conclusions of the studies. The quality assessment scale is shown in Supplementary Appendix 2. This checklist was based on previous metaanalyses and has been described elsewhere (Shepherd, Matheson, Laurens and Green, 2012; Chen et al., 2015). One author reviewed the included studies and determined a complete rating. The resulting scores were discussed between two investigators, and a consensus quality score was obtained.

Results

Studies included in the meta-analysis. Supplementary Appendix number 3 shows the data obtained in each study to describe each mediator variable for each analyzed paper. Table 1 shows the basic

descriptive statistics of the mediator variables. We want to highlight that the total number of patients analyzed assumes a significant number ($n = 1285$) and a control group ($n = 1279$). With regard to the techniques used to estimate connectivity networks, the most common are ALFF (20.68%) and ReHo (34.48%).

Meta-analysis Result. In Figures 2 and 3, the forest plot shows the effect size of each study, as well as the total mean of the effect size and a confidence interval of 95%. Conversely, if the effect size was negative, the patient group showed decreased activation compared to the healthy group. Therefore, we can see that the most significant positive effect size found is 1.715, with the upper limit being 2.448. On the other hand, the highest negative effect size is -1.673, with the lower limit being -2.361. Notably, in the case of negative differences, the work of Turner et al. (2013) and Fryer et al. (2015) show a lower width of the confidence interval, and the same work by Turner et al. (2013) shows the most accurate interval in the case of positive differences.

In this meta-analysis, people with schizophrenia did not show any hyperactivation compared to controls. However, they show decreased activation in the right precentral gyrus, specifically in the Brodmann area (BA) 4. In addition, they also show hypoactivation in the left superior temporal gyrus corresponding to BA 22. Thus, two clusters were found, one with 640 voxels and one with 150 voxels. The results are displayed in Table 2.

In addition, Figure 4 shows the graphical representation of the areas that are hypoactivated (visualized with BrainNet Viewer; Xia, Wang and He, 2013; <http://www.nitrc.org/projects/bnv/>). Note that the size of the node is proportional to the voxels it represents. That is, the larger the node, the more voxels there are in that area and the larger the region it represents. It is also worth noting that the nodes represented in blue correspond to the right precentral gyrus (BA 4), and the yellow nodes refer to the left superior temporal gyrus (BA 22).

Reliability analysis. A jackknife sensitivity analysis (Table 3) was carried out to check the replicability of the results. This analysis revealed that the right precentral gyrus (with coordinates of 50, -10, 40) was replicable in all 29/29 datasets (each dataset with one study left out) and that the left superior temporal gyrus (-58, -20, 4) was replicable in 26/29 datasets (the results were not confirmed only in 3 of the simulations performed, that is, 89.66% reliability). Therefore, we can establish a very high reliability of the results obtained.

Publication bias analysis. In Figures 5 and 6, we can see funnel plots wherein publication bias is graphically displayed. As we can see, the graphs suggest that there is no publication bias since the points (which correspond to the effect sizes of each study) are distributed uniformly on one side and on the other side of the value 0 of the abscises axis (effect size). Therefore, in our case, we can see how studies have been published with increasingly significant effects. In addition, Table 4 shows the values of Z statistics, as well as their significance ($p = .504$ and $p = .751$), which indicates that there is no bias.

Heterogeneity analysis. To determine the possible heterogeneity between the studies included in the present meta-analysis, Q and I^2 statistics were estimated. The results obtained are in (Table 5), where the values of tau (τ) representing the variance of the effect size distribution are displayed. In addition, we can see that Q statistics, from both positive and negative peaks, are statistically significant ($p < .001$). In this way, there is heterogeneity between the different studies, so it is appropriate to explore the mediator variables that could explain this phenomenon. On the other hand, it must be pointed out that the degree of heterogeneity is calculated by the I^2 index, as we can see are values that indicate a moderate degree of heterogeneity.

As mentioned above, the fact that there is heterogeneity between the studies included in the meta-analysis leads us to perform an analysis of possible mediator variables that could explain the variability between the effect sizes (here considered in absolute value). Since more than one statistically significant effect is present in some works, the effect size of each article analyzed is estimated by the mean of the effect size included in each paper. The following variables were explored: type of data analysis used in studies (ReHo, ALFF, fALFF, etc.), sample size, age, and sex of the patient group and control group, total, general, positive, and negative PANSS scores applied to the group of patients with schizophrenia, illness duration, and quality of the studies analyzed.

Categorical variables. First, Welch's t-test was used to analyze the relationship between the effect size and the type of analysis (ReHo or ALFF, the rest of the techniques were underrepresented and were eliminated from this analysis). The results indicate that there was a statistically significant relationship between the effect size and the type of analysis used ($t = -2.381$; $df = 13.927$; $p_{uni} = .016$; $r = .538$). In fact, the mean effect size in ReHo is $d = 1.242$, and in ALFF studies, $d = .964$, which suggests that studies using ReHo can obtain a greater effect size than those using ALFF, and this effect has high intensity according to Cohen's criteria.

Quantitative variables: Meta-regression analysis. A meta-regression was performed to analyze whether the quantitative variables described above (Table 1) had a statistically significant impact. Thus, Table 6 presents the minimum quadratic estimates of each meta-regression to evaluate the effect of each mediator variable on the estimate of the effect size.

From the above table, it follows that only sample sizes are statistically significant predictors of the effect size heterogeneity. The negative value of the regression coefficients indicates that works with higher sample sizes obtain lower values of the effect. In summary, the analysis performed with mediator variables indicates that, in the studies analyzed, the effect size is higher in ReHo estimated with smaller samples.

Discussion

To our knowledge, this is the first meta-analysis to study rs-fMRI in the whole brain in patients with schizophrenia compared to healthy people, including studies that use different analysis techniques. The results indicate that there was hypoactivation of the right precentral gyrus and left superior temporal gyrus in patients with schizophrenia compared to the control groups.

These results are congruent with other findings. Dong et al. (2018) also showed evidence in his meta-analysis (only ALFF studies) of a reduction in connectivity in the left superior temporal gyrus in patients with schizophrenia. Similarly, another meta-analysis also showed evidence of decreased ReHo in this area (Xiao et al., 2017). Additionally, in a systematic review, connectivity alterations were found in this area in studies performed with both rs-fMRI and task fMRI (Mwansisya et al., 2017). In addition, children of schizophrenic patients also show reduced activation of the left superior temporal gyrus during hearing comprehension (Rajarethinam et al., 2011). It should be noted that dysfunction in this region has been related to the presence of auditory hallucinations in patients with schizophrenia (Carter et al., 1994; Hugdahl, Løberg and Nygård, 2009). More specifically, Plaze et al. (2006) showed evidence that the anterior area of the left superior temporal gyrus is part of the brain network associated with the perception of auditory hallucinations in patients with schizophrenia, indicating that activity in this cortical region may be related to the severity of hallucinations. Activation of this area has also been demonstrated during the experience of auditory verbal hallucinations (Sommer et al., 2012). Consistent with our results, Gong et al. (2020) showed evidence of ALFF alteration in the right precentral gyrus. In addition, Li et al. (2019) found hypoconnectivity between the right precentral gyrus, which is involved in motor function, and the postcentral and precentral gyrus and cerebellum. Additionally, Xiao et al. (2017) showed evidence of decreased ReHo in the right central gyrus. In addition, hypoactivation in this area has been shown in relatives of people with schizophrenia compared to the control group (Scognamiglio and Houenou, 2014). It should be noted that dysfunctions in praxis networks in patients with schizophrenia, which includes the right precentral gyrus, correlate with deficits in the gesticulation of these patients (Wüthrich et al., 2020).

Our results are congruent with the meta-analysis of Gong et al. (2020), and we found that the duration of illness was not related to the effect size. Nevertheless, unlike the meta-analysis of Gong et al. (2020), we did not find that any of the PANSS scores were related to the effect size.

There are some limitations in this meta-analysis. First, we did not include those studies that did not report the coordinates or those that did not report the associated statistics. In addition, we have not taken into account the different subtypes of schizophrenia, which would be interesting for future research. Additionally, some analysis techniques used by the studies that we included were underrepresented and could not be taken into account when evaluating whether they could predict the effect size. There were several missing values regarding PANSS scores.

Finally, concerning the strengths of this work, it must be noted that a thorough search of articles by two independent researchers was carried out following the recommendations of PRISMA. In addition, no publication bias has been found. An analysis of the studies' quality was carried out, which is high. Just as the results obtained are highly reliable. They also support other findings, and in addition, new scientific and clinical contributions have been made to the knowledge, diagnosis and treatment of schizophrenia

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Tables

Table 1. *Descriptive statistics of the observed distributions of mediator quantitative variables.*

Mediator variables	Minimum	Maximum	Mean	Standard deviation
Illness duration	.446	16.948	4.003	4.980
Mean age schizophrenia group	13	40.050	26.650	7.732
Mean age control group	12.900	37.800	26.839	7.493
% men schizophrenia group	30.610	82.350	56.035	12.442
% men control group	39.540	82.350	56.204	11.285
Sample size schizophrenia group	14	168	44.31	37.179
Sample size control group	14	166	44.10	37.527
PANSS Total	19.240	49.120	38.019	7.899
PANSS Negative	8.410	27.490	19.601	4.200
PANSS Positive	9.530	27.530	19.297	4.801
PANSS General	37.290	102.000	79.457	15.269
Quality of the studies	9.50	11.00	10.760	.385

Table 2. *Major differences in activation between patients with schizophrenia and the control group in the present meta-analysis.*

Region	MNI coordinates			Z score	p value	Voxels	Brodmann's area
	x	y	z				
SQZ < HC							
Right precentral gyrus	50	-10	40	-5.902	.009	640	BA 4
Left superior temporal gyrus							
	-58	-20	4	-6.128	.009	150	BA 22

Table 3. *Jackknife sensibility analysis.*

All studies but...	Right precentral gyrus (50, -10, 40)	Left superior temporal gyrus (-58, -20, 4)
Alonso 1	Yes	Yes
Alonso 2	Yes	Yes
Bai	Yes	Yes
Ding	Yes	No
Fryer	Yes	No
Gao 1	Yes	Yes
Gao 2	Yes	Yes
Gao 3	Yes	Yes
Gou	Yes	Yes
Guo 1	Yes	Yes
Guo 2	Yes	Yes
Guo3	Yes	Yes
Li 1	Yes	Yes
Li 2	Yes	Yes
Li 3	Yes	Yes
Liang 1	Yes	Yes
Liang 2	Yes	Yes
Liao	Yes	Yes
Liu 1	Yes	Yes
Liu 2	Yes	Yes
Liu 3	Yes	Yes
Ren	Yes	Yes
Turner	Yes	No
Wang	Yes	Yes
Yan	Yes	Yes
Yu	Yes	Yes
Zhao	Yes	Yes

Zheng	Yes	Yes
Zhu	Yes	Yes

Yes: the region is reported if we extract the mentioned study of the analysis; No: the region is not reported if we extract the mentioned study of the analysis.

Table 4. *Publication bias assessment.*

Regions	<i>Z score</i>	<i>d.f</i>	<i>p value</i>
Right precentral gyrus	-.67	27	.504
Left superior temporal gyrus	-.22	27	.751

Z: contrast statistic of the publication bias, *d.f*: degree of freedom.

Table 5. *Heterogeneity analysis of the positive and negative peaks.*

Peaks	τ	<i>Q</i>	<i>d.f</i>	<i>p value</i>	I^2
Positives	0.051	44.805	21	.002	50.89
Negatives	0.071	70.336	26	< .001	61.61

τ : variance of effect-size distribution, *Q*: heterogeneity contrast statistic, *d.f*: degree of freedom, I^2 : rate of heterogeneity.

Table 6. *Meta-regression of the possible mediator variables and effect sizes.*

Variables	<i>Regression's coefficient B_i</i>	<i>p value</i>
Schizophrenia's sample size	-.008	< .001
Control's sample size	-.007	< .001
Schizophrenia's age	.007	.419
Control's age	.008	.385
Schizophrenia's gender	< .001	.993
Control's gender	.002	.755
PANSS total	.004	.373
PANSS positive	-.005	.754
PANSS negative	.016	.316
PANSS general	< .001	.979
Illness duration	.007	.631
Quality of the studies	.214	.272

Figures

Figure 1

Flow chart of the metanalysis search conducted.

Figure 2

Forest Plot of the positive effect size (interval's confidence of 95%)

Figure 3

Forest Plot of the negative effect size (interval's confidence of 95%)

Figure 4

Representation of the most significant coordinates (in blue the right precentral gyrus and yellow the left superior temporal gyrus) that show hypoactivation in patients with schizophrenia compared to healthy controls

Figure 5

Funnel Plot of the effect associated with the coordinate of the right precentral gyrus

Figure 6

Funnel Plot of the effect associated with the coordinate of the left superior temporal gyrus

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