1 Causality Mapping Using Resting-State fMRI reveals Suppressed Functional 2 Connectivity in Schizophrenia Patients

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15 **Short running title: Causality Mapping and Schizophrenia**

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4

1 **ABSTRACT**

2 Schizophrenia is a psychotic brain disorder in which patients exhibit aberrant
3 connectivity between different regions of the brain. Neuroimaging is a state-of-the-art
4 technique that is now increasingly been employed in clinical investigation of
5 Schizophrenia. In the present study, we have used resting-state functional magnetic
6 resonance neuroimaging (rsfMRI) to elucidate the cause-and-effect relationships
7 among four regions of the brain including occipital, temporal, and frontal lobes and
8 hippocampus in Schizophrenia. For that, we have employed independent component
9 analysis, a seed-based temporal correlation analysis, and Granger causality analysis
10 for measuring causal relationships amongst four regions of the brain in schizophrenia
11 patients. Eighteen subjects with nine patients and nine controls were evaluated in the
12 study. Our results show that Schizophrenia patients exhibit significantly different
13 activation patterns across the selected regions of the brain in comparison with the
14 control. In addition to that, we also observed an aberrant causal relationship between
15 these four regions of the brain. In particular, the temporal and frontal lobes of patients
16 with schizophrenia had a significantly lowered causal relationship with the other areas
17 of the brain. Taken together, the study elucidates the dysregulated brain activity in
18 Schizophrenia patients, decodes its causal mapping and provides novel insights
19 towards employment in clinical evaluation of Schizophrenia.

1 INTRODUCTION

2 Schizophrenia (SZ) is a chronic mental disorder affecting approximately 1% of the
3 global population (1). The condition is characterized by cognitive and behavioral
4 alterations, accompanied by hallucinations, delusions, and disorganized thinking (2,3).
5 SZ typically develops in young adults between the age of 18 and 35 (4) and has a
6 lifetime prevalence of 1% (4). Recent research on SZ has uncovered several genetic
7 and environmental factors that correlates with the development of the disease (4). An
8 increasing amount of experimental evidence is now suggesting that SZ induces
9 extensive alterations in the connectivity between various regions of the brain that
10 results in its functional dysregulation (5,6). Moreover, research studies have also
11 reported significant reductions in functional connectivity amongst various regions of
12 the brain in SZ patients (7–9). However, the type and scale of these disconnections,
13 suppressed functional connectivity and the underlying pathophysiological mechanisms
14 in SZ remain unclear (11).

15 Advancements in brain imaging techniques and protocols have now enabled scientists
16 to carry out in-depth investigations of the neuropathological mechanisms of SZ (10–
17 14). Several groundbreaking studies leveraging these technologies have helped reveal
18 a wide variety of abnormal structural and functional connections among anatomically
19 distant regions of the brain in SZ patients (15–18). Investigations using functional
20 brain imaging have helped elucidate reduced activation in the frontal, striatal, and
21 parietal regions during the performance of cognitive tasks in patients with SZ (19,20).
22 Furthermore, altered patterns of neural activation have been reported in the prefrontal
23 cortices, including the anterior cingulate cortex (ACC), the supplementary motor area
24 (SMA), the pre-SMA, the parietal cortex, and the subcortical basal ganglia nuclei (20–
25 23). Data from diffusion tensor imaging have highlighted reduced fractional
26 anisotropy (FA) in the internal capsule, thalamus, corpus callosum (CC), white matter
27 microstructures (24), and throughout the entire brain in patients with SZ (25).
28 Reduced FA in the CC has been associated with higher lateral ventricle (LV) volume,
29 while higher radial diffusivity (RD) values are associated with larger LV volume in
30 patients with SZ (26). This suggests that SZ may involve abnormalities in structural
31 white matter, which connects and activates different regions of the brain.

32 These findings have been supported and expanded upon by several neuroimaging
33 studies on functional connectivity (FC), which have elucidated temporal associations

1 between various regions of the brain (27). Specifically, this approach has been utilized
 2 to investigate disruptions in functional connectivity in brain of SZ patients (28).
 3 Previous studies have examined specific regions of the brain at resting state (29–31),
 4 and during sensory (32), and cognitive tasks (33) in patients with SZ. Reduced FC has
 5 been extensively reported in the neural pathways of patients with SZ, including the
 6 amygdala subregional-sensorimotor pathway (34), frontotemporal (35),
 7 thalamocortical (36), and cortico-cerebellar pathways (37). Differential FC in brain of
 8 patients with SZ and healthy controls, therefore, could have significant clinical
 9 implications, as psychopharmacological treatments could target aberrant FC in
 10 patients with SZ (39, 40). In addition, these differences could also be used as a
 11 neuroimaging biomarker to guide diagnoses of SZ (41, 42).

12 Towards this goal, in this work, we investigate the resting-state functional
 13 connectivity in brain of patients with SZ and examine the cause-and-effect
 14 relationships among these regions of the brain (38). For that, we have combined three
 15 different methods for analyzing FC, including (i) spatial independent component
 16 analysis (ICA) to identify the characteristics or features of fMRI data that are
 17 maximally independent, (ii) a seed-based temporal correlation analysis (SCA) to
 18 assess time-series associations and connections among regions, and (iii) Granger
 19 causality analysis (GCA) to analyze effective connectivity in the brain. In specific,
 20 spatial ICA is employed to extract the overall connectivity patterns at the whole-brain
 21 level and is used to elucidate the spatial structure of the blood-oxygen-level-dependent
 22 (BOLD) signal (47, 50, 51). The seed-based SCA was used to identify regions, or
 23 “seeds,” that correlate with FC and activity in other seeds or regions using time series
 24 of BOLD signals from seed-voxels and other regions (41–44). Lastly, the GCA was
 25 used to study the bidirectional effects between two variables in a time series (45) to
 26 examine time-lagged causal effects on specific regions of the brain by using time
 27 predictions between an fMRI time series (46,47). The approach helped identify the
 28 dynamic causal interactions between the four selected regions of the brain. Our results
 29 show that the brains of patients with SZ exhibit aberrant activation patterns in the HC,
 30 OL, TL, and FL. Moreover, the functional and structural connectivity among these
 31 four regions differs significantly in patients with SZ, which has been validated by the
 32 VAR models using Granger causality. Last, our causal analysis through mediation
 33 revealed significant differences in decision making in patients with SZ.

1 Taken together, this study expands our understanding of the resting-state FC (rsFC) in
2 patients with SZ at the whole-brain level and reports the aberrations in FC among
3 multiple regions of the brain using a combination of statistical approaches. The study
4 also helps characterize the direction of FC among different regions of the brain and
5 how it differs in patients with SZ from healthy controls (39) thereby providing
6 valuable insights into the neural basis of SZ (39).

1 METHODOLOGY

2 2.1 Granger causality

3 We used a Granger causality (G-causal) test and VAR modeling to analyze the fMRI
4 data. This method determines the causal relationships between two variables. If a
5 variable x has a G-causal relationship with another variable y , then the lag values of x
6 can be used to forecast the future values of y and vice versa. This study examined the
7 causal relationships among four regions of the brain: the frontal, occipital, and
8 temporal lobes and the hippocampus.

9 Mathematical Formulation of Granger Causality

10 Consider two random variables X_t, Y_t . Assume a lag length of p . For example, y is
11 occipital lobe and X is temporal lobe. For occipital and temporal lobes, the model
12 could be written as:

$$13 \quad T_t = c_1 + a_1 T_{t-1} + a_2 T_{t-2} + \dots + a_p T_{t-p} + b O_{t-1} + b O_{t-2} + \dots + b O_{t-p} + e_t$$

14 Estimate by OLS and test for the following hypothesis:

$$15 \quad \begin{aligned} H_0 : \beta_1 = \beta_2 = \dots = \beta_p &= 0 \\ H_1 : any \beta &\neq 0 \end{aligned}$$

16 To check if occipital lobe does granger-cause to temporal lobe or not, here we will
17 take y as a occipital lobe 'o' and x as a temporal lobe 't'.

18 Unrestricted sum of squared residual:

$$19 \quad RSS_1 = \sum_t \hat{a}_t^2$$

20 Restricted sum of square residual:

$$21 \quad RSS_2 = \sum_t \hat{a}_t^2$$

$$22 \quad F = \frac{(RSS_2 - RSS_1)}{RSS_1 / (T - 2p - 1)}$$

1 Under general condition, the OLS estimate is given by,

$$b = \left[\sum_{i=1}^T (o_i o_i') \right]^{-1} \left[\sum_{i=1}^T (o_i t_i) \right]$$

2 assuming that the $(k \times k)$ matrix $\sum_{i=1}^T (o_i o_i')$ is nonsingular the OLS sample residual for

$$u_i = t_i - o_i' b \quad t_i - o_i' \beta + \mu_i$$

3 observation t is $t_i - o_i' \beta + \mu_i$. Often the model is written in matrix
4 notation as

5 $T = O\beta + \mu$ Where

$$T_{(T \times 1)} = \begin{bmatrix} t_1 \\ t_2 \\ \vdots \\ t_T \end{bmatrix} \quad O_{(T \times k)} = \begin{bmatrix} o_1' \\ o_2' \\ \vdots \\ o_T' \end{bmatrix} \quad u_{(T \times 1)} = \begin{bmatrix} u_1' \\ u_2' \\ \vdots \\ u_T' \end{bmatrix}$$

6
7 Then the OLS estimate in $b = \left[\sum_{i=1}^T (o_i o_i') \right]^{-1} \left[\sum_{i=1}^T (o_i t_i) \right]$ can be written as

$$b = \left\{ \begin{bmatrix} o_1' \\ o_2' \\ \vdots \\ o_T' \end{bmatrix} \right\}^{-1} \left\{ \begin{bmatrix} t_1 \\ t_2 \\ \vdots \\ t_T \end{bmatrix} \right\}$$

$$= (O'O)^{-1} (O'T)$$

8
9
10 Similarly, residual can be written as:

$$u = t - Ob = t - O(O'O)^{-1} O'T = [I_T - O(O'O)^{-1} O'] t = M_x u$$

11
12 Where M_x is defined as the following $(T \times T)$ matrix $M_x = I_T - O(O'O)^{-1} O'$. One can
13 readily verify that $M_x = M_x'$ where idempotent $M_x M_x = M_x$ and the orthogonal to the
14 columns of O . $M_x X = 0$. OLS sample residuals are orthogonal to the explanatory variables in
15 O and population residual can be found by substituting $u = M_x (O\beta + u) = M_x u$. The

1 difference between the OLS estimate b and the true population parameter β is found by

$$b = \left\{ \begin{bmatrix} o_1 & o_2 & \dots & o_T \end{bmatrix} \begin{bmatrix} o'_1 \\ o'_2 \\ \vdots \\ o'_T \end{bmatrix} \right\}^{-1} \left\{ \begin{bmatrix} o_1 & o_2 & \dots & o_T \end{bmatrix} \begin{bmatrix} t_1 \\ t_2 \\ \vdots \\ t_T \end{bmatrix} \right\}$$

2 substituting $T = O\beta + \mu$ into

$$b = (O'O)^{-1} O' [O\beta + u] = \beta + (O'O)^{-1} Xu$$

4 Now estimate the F test (Wald test) about beta under assumption. A Wald test of H_0 is based

5 on the following results. Consider an $(n \times 1)$ vector $z \sim N(0, \Omega)$ with non-singular then

$$6 \quad Z' \Omega^{-1} Z \sim \chi^2_{(n)}$$

$$\begin{aligned} Z' \Omega^{-1} Z &= Z' (P \wedge P')^{-1} Z \\ &= z' [P']^{-1} \wedge^{-1} P^{-1} z \\ &= [P^{-1} z]' \wedge^{-1} P^{-1} z \\ &= w' \wedge^{-1} w \\ &= \sum_{i=1}^n w_i^2 / \lambda_i \end{aligned}$$

7

8 Where $w = P^{-1} z$ and w is Gaussian with mean zero and variance

$$9 \quad E(w w') = E(P^{-1} z z' [P']^{-1}) = P^{-1} \Omega [P']^{-1} = P^{-1} P \wedge P' [P']^{-1} = \wedge. \text{ Thus } w' \wedge^{-1} w \text{ is}$$

10 the sum of squares of n independent normal variables each divided by its variance λ . It

11 accordingly has a χ^2_n distribution as claimed. Applying proposition directly to

$$12 \quad Rb \sim N(r, \sigma^2 R(O'O)^{-1} R') \text{ under } H_0 \quad (Rb - r)' [\sigma^2 R(O'O)^{-1} R']^{-1} (Rb - r) \sim \chi^2_m$$

13 Replacing σ with the estimate s and dividing by the number of restriction gives the Wald form

$$14 \quad \text{of the OLS F test of a linear hypothesis. } F = (Rb - r)' [s^2 R(O'O)^{-1} R']^{-1} (Rb - r) / m$$

$$15 \quad F = \frac{(Rb - r)' [\delta^2 R(O'O)^{-1} R']^{-1} (Rb - r) / m}{[RSS / (T - K)] \delta^2}$$

16 The numerator is a χ^2_m variable divided by its degree of freedom while the denominator is

17 $\chi^2_{(T-k)}$ variable divided by its degree of freedom again since b and μ are independent, the

18 numerator and denominator are independent of each other hence

1 $F = (Rb - r)'[s^2 R(O'O)^{-1} R']^{-1} (Rb - r) / m$ has an exact F(m, T-K) distribution under Ho.

2 Let b denote the unconstrained OLS estimate and let RSS_1 be the residual sum of square

3 $RSS_1 = \sum_{t=1}^T (t_t - o_t' b)^2$ resulting from using this estimate. Let b^* denote the constrained

4 OLS estimate and RSS_0 the residual sum squares from the constrained OLS estimation.

5 $RSS_0 = \sum_{t=1}^T (t_t - o_t' b^*)^2$. Then the Wald form of the F test of a linear hypothesis

6 $F = (Rb - r)'[s^2 R(O'O)^{-1} R']^{-1} (Rb - r) / m$ can equivalently be calculated as

$$F = \frac{(RSS_0 - RSS_1) / m}{RSS_1 / (T - K)}$$

8 Vector auto regression (VAR) model

9 VAR models are used for estimating and forecasting in time series data. In
10 multivariate time series analysis, it is one of most easy to use technique. It is known as
11 extension of AR model. One of crucial step in VAR is selection of lags for lag
12 selection we have three criteria's AIC BIC HQIC.

$$\begin{aligned} t_t &= b_{10} - b_{12} o_t + v_{11} t_{t-1} + v_{12} o_{t-1} + \epsilon_t \\ o_t &= b_{20} - b_{21} t_t + v_{21} t_{t-1} + v_{22} o_{t-1} + \epsilon_t \end{aligned}$$

14 In above model 'o' represent the occipital lobe and 't' represent the temporal lobe.
15 VAR models are used for forecasting in time series but we can employ them to check
16 the Granger causality of the variables. One of the important steps in VAR model is the
17 selection of lag length which is based on specific criteria.

19 Data

20 The study was approved by the Institutional Review Board of King Khalid University
21 Hospital. The participants included a selection of 15 healthy controls and 15 patients
22 with SZ. From these, we selected 18 subjects (9 controls and 9 patients with SZ). All
23 participants underwent the same number of scans according to our study requirements.
24 The participants were aged 33.14 ± 9.96 (mean $\pm$ SD) years. The SZ participants were
25 recruited through local psychiatric clinics, and the controls were recruited from
26 hospital volunteers. All participants provided informed written consent before

1 participating. All SZ and control subjects were outpatients and had been clinically
2 stable for at least two weeks prior to the study. The SZ participants were diagnosed by
3 a research psychiatrist based on the DSM.IV criteria; the diagnoses were confirmed by
4 a trained research assistant.

5 Written informed consent was obtained from subjects which was approved by the
6 Institutional Review Board (IRB) at King Khalid University Hospital (KKUH). All
7 procedures were conducted according to the Declaration of Helsinki.

8

1 **3. RESULTS**

2 **3.1. The brains of patients with SZ exhibit aberrant activation patterns in the** 3 **hippocampus (HC), occipital lobe (OL), temporal lobe (TL), and frontal lobe** 4 **(FL)**

5 To evaluate differences in brain activation patterns in patients with SZ, we obtained
6 fMRI scans of nine subjects with SZ (**Supplementary Data 1**). Nine clinically
7 healthy individuals were also scanned and used as controls (**Supplementary Data 2**).
8 The resulting fMRI scan data were pre-processed for realignment, spatial
9 normalization, smoothing, and co-registration using statistical parametric mapping
10 (SPM12) (48) (**Figures 1A, B**). We then compared activation levels in four regions of
11 interest (ROIs): the hippocampus (HC), the occipital lobe (OL), the temporal lobe
12 (TL) and the frontal lobe (FL). Brain activation in patients with SZ was compared to
13 that of the controls using two independent sample *t*-tests (49). We found that average
14 brain activity in the two groups differed significantly in the HC ($t(798) = 125.254$, p
15 < 0.05), the OL ($t(798) = 43.573$, $p < 0.05$), the TL ($t(798) = 130.784$, $p < 0.05$), and
16 the FL ($t(798) = -9.774$, $p < 0.05$) (**Figure 1C**). We conclude that patients with SZ
17 have significantly less activation in the HC, the OL, and the TL than healthy controls
18 (59). However, we also observed significantly higher activation in the FL of patients
19 with SZ.

20 **3.2. Functional connectivity among the HC, OL, TL, and FL differs significantly** 21 **in patients with SZ**

22 The human brain is a complex neuronal network with variable levels of FC among
23 different regions. FC gives rise to the physiological functions of different regions of
24 the brain. Having observed significant variation in the activation of the four ROIs, we
25 then evaluated the effect of this activation on the FC among these ROIs (28). To do
26 this, we quantified the FC among the four ROIs by computing the Pearson correlations
27 for the SZ and control groups (Figures 2A, B). For the controls, the highest positive
28 correlation was observed between the FL and the TL ($r = 0.85$, $p < 0.05$) while the
29 lowest positive correlation was between the FL and the OL ($r = 0.63$, $p < 0.05$)
30 (Figure 2A). The smallest negative correlation in the controls was observed between
31 the HC and the TL ($r = -0.06$), while the largest negative correlation was between the
32 HC and the OL ($r = -0.01$). For the SZ groups, the highest positive correlation was

1 observed between the FL and the TL ($r = 0.79$, $p < 0.05$), while the lowest positive
2 correlation was between the FL and the OL ($r = -0.26$) (Figure 2B). The smallest
3 negative correlation was between the HC and the TL ($r = 0.17$, $p < 0.05$), while the
4 largest negative correlation was between the HC and the OL ($r = 0.42$, $p < 0.05$).
5 These results indicate that the functional connectivity network is significantly altered
6 in patients with SZ (Figures 2C, D).

7 **3.3 Patients with SZ exhibit aberrant structural connectivity in the ROIs**

8 Next, to investigate the temporal variations in FC patterns (or *effective structural*
9 *connectivity*) among the four ROIs, we employed the vector auto regression (VAR)
10 model (51) at times $t-2$, $t-1$, and t . Between $t-1$ and t , the HC exhibited strong causal
11 connectivity with the OL ($\hat{\beta}^c = 0.15$, $p < 0.05$) and with the TL ($\hat{\beta}^c = -0.2$, $p < 0.05$) in
12 healthy individuals. In patients with SZ, these connections of the HC with the OL and
13 the TL were completely inhibited (Figure 3; Tables 1, 2). The TL also had strong
14 causal connectivity with the HC ($\hat{\beta}^c = -0.05$, $p < 0.05$) and the OL ($\hat{\beta}^c = 0.12$, $p < 0.05$)
15 in the controls; these connections were also deregulated in the SZ group. The OL had
16 causal connectivity with the FL ($\hat{\beta}^c = 0.78$, $p < 0.05$) and vice versa ($\hat{\beta}^c = -0.07$, $p <$
17 0.05), and the OL had causal connectivity with the TL ($\hat{\beta}^c = 0.09$, $p < 0.05$) in the
18 controls; these connections did not appear in patients with SZ. Furthermore, at lag
19 times $t-1$ and $t-2$, the HC exhibited significantly diminished FC in patients with SZ.
20 This differed from the controls most remarkably at lag $t-2$. Interestingly, at $t-1$ and $t-2$,
21 the FL and OL showed enhanced anomalous connectivity in patients with SZ. The TL
22 maintained its effective structural connectivity in both the controls and the patients
23 with SZ at lag $t-2$.

24 **3.4 Validation of VAR models using Granger causality**

25 To validate the structural model of the brain connectivity network obtained through
26 VAR, we further employed a G-causal test (44) to examine the bidirectional causal
27 effects of the ROIs on each other in patients with SZ and in the controls. In the
28 controls (Table 3) the OL and TL regions had significant G-causality with the HC
29 (Figure 4A). Moreover, the HC and the FL were G-causal for OL activation (Figure
30 4B), while the OL and the FL had G-causality with the TL (Figure 4C). In the
31 controls, the TL also had G-causality with the FL (Figure 4D). However, we observed
32 weaker causal relations among the four ROIs in patients with SZ (Table 4) than in the

1 controls. Specifically, the HC was not G-causal for the other ROIs in patients with SZ
 2 (Figure 4A). However, the TL and the HC continued to have a significant G-causal
 3 relationship with the OL (Figure 4B). Moreover, the OL was G-causal for the TL
 4 (Figure 4C), while the OL and the TL were G-causal for the FL (Figure 4D). Taken
 5 together, these findings confirm our earlier hypotheses on aberrant patterns and
 6 reduced activation in the four ROIs in patients with SZ.

7

8 **3.5 Causal analysis through mediation reveals differences in decision making in** 9 **patients with SZ**

10 To investigate differences in the decision-making processes of patients with SZ, we
 11 performed a causal analysis of HC mediation. To do this, we analyzed the role of the
 12 HC as a mediator between the FL and OL in the controls and in patients with SZ
 13 (Figure 5). Our results show that the HC played a significant role in the patients with
 14 SZ (Figure 5B) but was non-significant in the control group (Figure 5A). We further
 15 observed that the FL disturbed the activity of the OL and the HC in patients with SZ,
 16 while in the controls this effect was non-significant (Table 5).

17

18

1 4. DISCUSSION

2 This study examined rsFC in patients with SZ on a whole-brain scale. The results
 3 show that the parietal region has less connectivity to bilateral DLPFC, while the
 4 parietal and frontal regions have strong connectivity in patients with SZ. Our results
 5 also showed that patients with SZ exhibited significantly less activation in the HC, the
 6 OL, and the TL than healthy controls (61), while the FL showed significantly more
 7 activation in patients with SZ. Abnormal functional connectivity in the prefrontal
 8 cortex may reflect psychopathologies such as an inability to allocate internal or
 9 external attentional resources, a crucial skill for goal-oriented behaviors (61, 62).
 10 Working memory and decision-making deficits have also been repeatedly reported in
 11 patients with SZ; these symptoms are often linked to abnormal functioning of the
 12 prefrontal cortex (63, 64). Temporal hallucinations and delusions are the main
 13 characteristics of SZ; these are mainly attributed to aberrant FC in the temporal cortex
 14 (65, 66). There is also a well-established link between SZ and the hippocampus, a
 15 complex region of the brain that plays a critical role in multiple cognitive domains,
 16 including memory, imagination, and emotions (67, 68), that are known to be impaired
 17 in patients with SZ (69).

18 Approaches such as spatial independent component analysis (ICA), seed-based
 19 temporal correlation analysis (SCA) and Granger causality analysis (GCA) can be
 20 used to explore the activity and functions of the intrinsic neuronal network using
 21 rsfMRI data (70–73). Our findings are consistent with those of other studies. For
 22 example, one study by (74) observed reduced degree centrality (DC) of the bilateral
 23 putamen nuclei in patients with SZ compared to controls. DC is an index used to
 24 identify the regions of the brain (at the whole-brain level) that display functional
 25 deficits in patients with SZ. That study also observed a lack of causal connectivity
 26 between the putamen and multiple regions of the default mode network (DMN), the
 27 orbital area of the inferior frontal cortex, and the right fusiform in patients with SZ. In
 28 addition, a previous study found abnormal rsFC in the amygdala subregional-
 29 sensorimotor regions of the brain in patients with SZ; this abnormality was also
 30 associated with positive symptoms in patients with SZ (75). A similar pattern of
 31 altered rsFC has been observed throughout the entire brain in patients with SZ.
 32 Disrupted pathways from the limbic areas to the thalamus have also been
 33 demonstrated using resting-state effective connectivity (rsEC) analysis (76).

1 Furthermore, a wide range of alterations to thalamic nuclei functional connectivity
2 have been observed in the cortico-cerebellar-thalamo-cortical circuit pathways of
3 patients with SZ (77). A systematic review of task and rsfMRI studies demonstrated
4 the convergence of brain neural dysfunction between tasks and rsfMRI abnormalities
5 in the prefrontal regions, including the dorsal lateral prefrontal cortex, the orbital
6 frontal cortex, and the TL, particularly the superior temporal gyrus (78). Together,
7 these previous findings demonstrate that patients with SZ exhibit altered FC and
8 effective connectivity (EC) among large regions of the brain. Moreover, brain rsFC
9 and rsEC can be used as diagnostic markers for SZ and might be implicated in
10 therapeutic interventions as well.

11 A major strength of this study is its use of a combination of three different FC analysis
12 methods to investigate functional disconnections between various regions of the brain.
13 However, the study does have some limitations, which should be considered when
14 interpreting the results. Most significantly, the sample size in the present study is
15 small. Additional longitudinal follow-up studies with larger samples are needed to
16 elucidate the alterations in FC between regions of the brain in patients with SZ.

17 **Conclusion:** GCA is a useful tool for characterizing the functional direction of time-
18 series data. GCA has broad implications in the neurosciences and neuroimaging
19 because of the importance of the FC of different regions of the brain during tasks.
20 GCA can be used to characterize the significant functional directions of different
21 regions of the brain. In the above diagram, the functional direction of different regions
22 of the brain are indicated by arrows. These arrows illustrate the significant Granger
23 causes in the patients with SZ (red) and the control subjects (black) in our study. We
24 can conclude that, in patients with SZ, some regions of the brain are less active than
25 those of healthy subjects during task performance.

26

27 **Ethical publication statement:** We confirm that we have read the Journal's position
28 on issues involved in ethical publication and affirm that this report is consistent with
29 those guidelines.

30

31 **Disclosure**

32 Neither of the authors has any conflict of interest to disclose

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1 **FIGURE LEGEND:**

2 **Figure 1 –Brain Activation in Schizophrenia Patients in Comparison with**
 3 **Healthy Individuals.** Axial slices of activations in HC, TL, OL, and FL of: (A)
 4 healthy individuals (control), and (B) schizophrenia patients, at resting state. (C) Bar
 5 chart of average activations in ROIs for control and patients.

6 **Figure 2 - Correlation Between ROIs in Schizophrenia.** Person correlation between
 7 ROIs in (A) Control, (B) Schizophrenia patients. Connectivity in ROIs in (C) Control,
 8 and (D) Schizophrenia patients, using BrainNet Viewer (52).

9 **Figure 3 – Structural Connectivity in ROIs.** (A) Significant causality links in
 10 control between HC, OL, FL and TL, (B) Significant causality links in patients
 11 between HC, OL, FL and TL.

12 **Figure 4– Structural Connectivity in ROIs obtained through Granger Causality**
 13 **for HC, OL, TL, and FL.** Blue and Red arrows show significant granger causality
 14 between ROIs for the control case and SZ patients, respectively.

15 **Figure 5 – Mediation Analysis in ROIs.** (A) Significant mediation in control
 16 between HC, OL, and FL, (B) Significant mediation in patients between HC, OL, and
 17 FL.

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1 **TABLE LEGEND:**

2 **Table 1 - Estimated VAR Model for Control.** “*Mod (1-4) at lag1*” is the VAR
 3 model till lag 1, $\hat{\beta}_{t-1}^c$ is the coefficient of variation for control case at lag 1, $\hat{\beta}_{t-2}^c$ is
 4 coefficient of variation for control case at lag 2, t is the test statistic, S.E is the
 5 standard error of the model, p value is the probability of obtaining test results by
 6 chance.

Mod (1-4) at lag1	$\hat{\beta}_{t-1}^c$	S.E	t	p	Mod (1-4), at lag 2	$\hat{\beta}_{t-2}^c$	S.E	t	p
HC(t) $\leftarrow$ HC (t-1)	0.51	0.05	10.15	0.000	HC(t-2)	0.17	0.05	3.4	0.001
HC(t) $\leftarrow$ OL (t-1)	0.15	0.07	2.14	0.032	OL(t-2)	-0.17	0.07	-2.5	0.011
HC(t) $\leftarrow$ FL (t-1)	-0.00	0.09	-0.08	0.937	FL(t-2)	0.03	0.09	0.3	0.714
HC(t) $\leftarrow$ TL (t-1)	-0.20	0.07	-2.62	0.009	TL(t-2)	0.16	0.07	2.1	0.036
OL(t) $\leftarrow$ HC (t-1)	-0.05	0.03	-1.35	0.178	HC(t-2)	-0.02	0.03	-0.7	0.478
OL(t) $\leftarrow$ OL (t-1)	0.73	0.05	13.61	0.000	OL(t-2)	0.01	0.05	0.2	0.832
OL(t) $\leftarrow$ FL (t-1)	0.22	0.07	3.16	0.002	FL(t-2)	-0.11	0.07	-1.6	0.098
OL(t) $\leftarrow$ TL (t-1)	0.04	0.05	0.75	0.456	TL(t-2)	0.04	0.06	0.7	0.453
FL(t) $\leftarrow$ HC (t-1)	-0.01	0.03	-0.60	0.547	HC(t-2)	-0.00	0.03	-0.2	0.777
FL(t) $\leftarrow$ OL(t-1)	-0.07	0.04	-1.66	0.098	OL(t-2)	0.05	0.04	1.1	0.234
FL(t) $\leftarrow$ FL (t-1)	0.78	0.05	14.15	0.000	FL(t-2)	0.03	0.05	0.6	0.495
FL(t) $\leftarrow$ TL (t-1)	0.09	0.04	2.02	0.043	TL(t-2)	0.01	0.04	0.4	0.681
TL(t) $\leftarrow$ HC (t-1)	-0.05	0.03	-1.66	0.097	HC(t-2)	0.01	0.03	0.4	0.644
TL(t) $\leftarrow$ OL (t-1)	0.12	0.04	2.58	0.010	OL(t-2)	-0.11	0.04	-2.3	0.020
TL(t) $\leftarrow$ FL (t-1)	0.07	0.06	1.15	0.251	FL(t-2)	0.03	0.06	0.6	0.541
TL(t) $\leftarrow$ TL (t-1)	0.67	0.05	12.46	0.000	TL(t-2)	0.11	0.05	2.1	0.035

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8 **Table 2 - Estimated VAR Model for Schizophrenia Patients.** “*Mod (1-4) at lag1*”
 9 is the VAR model till lag 1, $\hat{\beta}_{t-1}^p$ is the coefficient of variation for patients at lag 1,
 10 $\hat{\beta}_{t-2}^p$ is coefficient of variation for patients at lag 2, t is the test statistic, S.E is the
 11 standard error of the model, p value is the probability of obtaining test results by
 12 chance.

Mod (1-4) at lag1	$\hat{\beta}_{t-1}^p$	S.E	t	p	Mod (1-4), at lag 2	$\hat{\beta}_{t-2}^p$	S.E	t	p
HC(t) $\leftarrow$ HC (t-1)	0.36	0.05	6.34	0.000	HC(t-2)	0.29	0.05	5.0	0.000
HC(t) $\leftarrow$ OL (t-1)	0.10	0.06	1.69	0.091	OL(t-2)	-0.01	0.06	-0.2	0.820
HC(t) $\leftarrow$ FL (t-1)	-0.00	0.07	-0.10	0.917	FL(t-2)	0.03	0.07	0.4	0.638
HC(t) $\leftarrow$ TL (t-1)	0.10	0.07	1.38	0.166	TL(t-2)	-0.11	0.07	-1.5	0.129
OL(t) $\leftarrow$ HC (t-1)	0.09	0.04	1.96	0.050	HC(t-2)	-0.10	0.04	-2.04	0.042
OL(t) $\leftarrow$ OL (t-1)	0.62	0.05	11.8	0.000	OL(t-2)	0.07	0.05	1.45	0.148
OL(t) $\leftarrow$ FL (t-1)	-0.01	0.06	-0.22	0.826	FL(t-2)	0.03	0.06	0.58	0.562

OL(t) ← TL (t-1)	0.02	0.06	0.33	0.745	TL(t-2)	0.10	0.06	1.70	0.089
FL(t) ← HC (t-1)	-0.03	0.04	-0.65	0.513	HC(t-2)	0.05	0.04	1.14	0.256
FL(t) ← OL (t-1)	0.13	0.05	2.65	0.008	OL(t-2)	-0.02	0.05	-0.40	0.693
FL(t) ← FL (t-1)	0.31	0.06	5.10	0.000	FL(t-2)	0.25	0.06	4.21	0.000
FL(t) ← TL (t-1)	0.14	0.06	2.39	0.017	TL(t-2)	-0.01	0.06	-0.27	0.789
TL(t) ← HC (t-1)	-0.06	0.04	-1.47	0.142	HC(t-2)	-0.01	0.04	-0.30	0.768
TL(t) ← OL (t-1)	0.03	0.04	0.76	0.449	OL(t-2)	0.09	0.04	1.93	0.053
TL(t) ← FL (t-1)	0.02	0.05	0.46	0.073	FL(t-2)	-0.06	0.05	-1.13	0.259
TL(t) ← TL (t-1)	0.69	0.05	12.3	0.000	TL(t-2)	0.21	0.05	3.86	0.000

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2 **Table 3: Granger Causality Wald Test for Control.** Equation is a dependent
3 variable while excluded is representing independent variable, χ^2 is a test of
4 association, df stands for degree of freedom, Prob> χ^2 is the probability value for
5 drawing conclusion about null hypothesis.

Equation	Excluded	Chi ²	df	Prob>chi ²
HC	OL	6.628	2	0.036
	FL	0.223	2	0.894
	TL	6.970	2	0.031
	ALL	13.056	6	0.042
OL	HC	6.265	2	0.044
	FL	11.206	2	0.004
	TL	3.815	2	0.148
	ALL	30.024	6	0.000
FL	HC	1.171	2	0.557
	OL	2.751	2	0.253
	TL	10.839	2	0.004
	ALL	15.068	6	0.020
TL	HC	3.450	2	0.178
	OL	7.001	2	0.030
	FL	6.353	2	0.042
	ALL	19.55	6	0.003

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7 **Table 4 – Granger Causality Wald Test for Patients.** Equation is a dependent
8 variable while excluded is representing independent variable χ^2 is a test of
9 association, df stands for degree of freedom, Prob> χ^2 is the probability value for
10 drawing conclusion about null hypothesis.

Equation	Excluded	Chi ²	df	Prob>chi ²
HC	OL	3.977	2	0.137
	FL	0.231	2	0.891
	TL	2.383	2	0.304
	ALL	10.302	6	0.112
OL	HC	5.218	2	0.074
	FL	0.337	2	0.845
	TL	10.669	2	0.005

	ALL	29.205	6	0.000
FL	HC	1.294	2	0.524
	OL	9.596	2	0.008
	TL	13.135	2	0.001
	ALL	38.862	6	0.000
TL	HC	3.747	2	0.154
	OL	10.069	2	0.007
	FL	1.273	2	0.529
	ALL	13.544	6	0.035

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2 **Table 5 – Mediation Analysis for Regions of Interest.** S.E. stands for standard error,
3 C.R. is the confidence ratio and P is the probability value.

Control	Dependent	Effect	Independent	Estimate	S.E.	C.R.	P
	HC	<---	OL	-0.048	0.045	-1.062	0.288
	FL	<---	OL	0.476	0.035	13.791	***
	FL	<---	HC	0.225	0.038	5.904	***
Patients	Dependent	Effect	Independent	Estimate	S.E.	C.R.	P
	HC	<---	OL	0.39	0.038	10.333	***
	FL	<---	OL	0.464	0.035	13.098	***
	FL	<---	HC	0.361	0.042	8.676	***

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HC

OL

TL

FL

A**Control** **B****Patients**