Schizophrenia Research 231 (2021) 10–12

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

From local to global and back: An exploratory study on cross-scale desynchronization in schizophrenia and its relation to thought disorders

Keywords:
Schizophrenia spectrum
Thought disorders
Resting state fMRI
ReHo - regional homogeneity
Functional connectivity
Global signal correlation
Spatiotemporal psychopathology

To the Editors

Thought disorders (delusions and conceptual disorganization) are core positive symptoms of schizophrenia and psychosis. Clinically, it has been proposed that delusions are generated by incoherent subjective experiences (Parrott, 2019) which, in turn, prevent the coherent synchronization of environmental with self-generated stimuli (Damiani et al., 2020). The dysconnectivity hypothesis supports this view (Friston and Frith, 1995), and has been confirmed by solid neuroimaging findings (Dong et al., 2018). In fMRI, local reductions in connectivity linked to schizophrenia symptoms have been operationalized via Regional Homogeneity (ReHo, measuring correlation between neighbour voxels) (Xu et al., 2015), alterations on the global level of brain activity can be measured via GScorr (i.e. the correlation between a single region's activity and the Global Signal) (Scalabrini et al., 2020b; Zhang et al., 2020). What remains unclear is how dysconnectivity occurs across different spatial scales, that is, "cross-scale desynchronization", as we say. To test relationship and, specifically, synchronization between local and global scales in schizophrenia, we investigated local ReHo in intimate connection to local-to-global brain activity as measured by GScorr.

Our primary aim was to test whether cross-scale desynchronization could be quantified by the strength of association of local (ReHo) with local-to-global (GScorr) connectivity. The guiding question here was: are the regional changes in ReHo truly independent of global GScorr changes or, as we hypothesized, are they related to changes in the brain's global activity? Furthermore, assuming cross-scale desynchronization as key for psychopathological symptoms, we predicted that local-to-global dysconnectivity, rather than local dysconnectivity (Scalabrini et al., 2020a), would be associated with thought disorders severity.

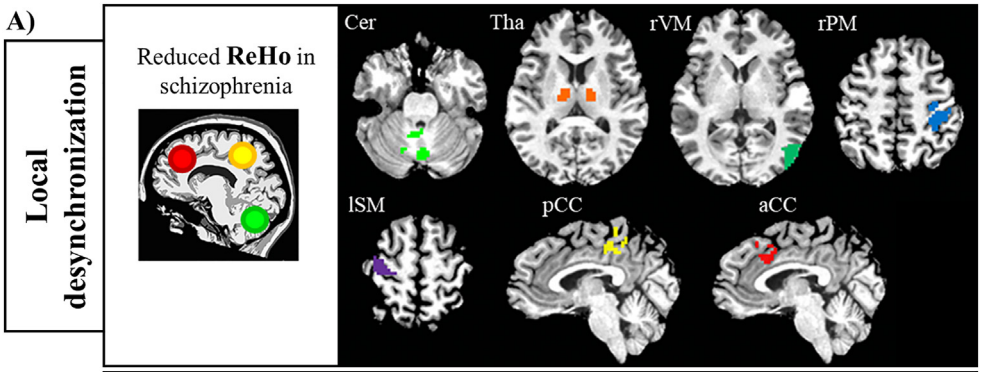
We analyzed resting-state scans from two samples including both healthy neurotypical (TYP) and schizophrenic (SCH) subjects. The first sample consisted of 18 TYP and 18 SCH from the TMU-ShuangHo Hospital, New Taipei City. The second sample consisted of 51 TYP and 34 SCH from the Center for Biomedical Research Excellence open-access dataset, (COBRE: http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html). Detailed descriptions of sample characteristics, preprocessing, main/control analyses and limitations can be found in Supplementary Materials.

First, we conducted a whole-brain, voxel-wise analysis to identify regions with different ReHo in SCH versus TYP group. 7 regions showed differences in both samples, all with reduced ReHo in SCH (FDR-corrected $p = 0.05$; cluster size >50 voxels) (Fig. 1A). Secondly, we considered all subjects and measured GScorr for each of the 7 regions. Right-PreMotor cortex (rPM) and posterior-cingulate (pCC) showed reduced GScorr in SCH (Fig. 1B). Thirdly, we measured the correlation of ReHo and GScorr from the same region to test the interdependence of local and global activity as a proxy of cross-scale desynchronization. Again, ReHo and GScorr showed positive correlation in rPM and pCC (Fig. 1C). Fourth, correlations with symptoms were tested for ReHo and GScorr in rPM and pCC (Fig. 1D). GScorr, and not ReHo, was significantly associated to thought disorders severity (as measured by items P1 and P2 of the Positive and Negative Symptoms Scale) (PANSS Kay et al., 1989). The analyses have been retested after GS regression to assess the impact of GS on the local and global measures including their cross-scale dynamics.

The bulk of the novel evidence provided by our study comprises several findings: 1) In addition to the local, within-level dysconnectivity measured by ReHo, a local-to-global dysconnectivity is present (GScorr reduced in SCH); 2) Local and local-to-global dysconnectivity are associated with specific regions (rPM and pCC); 3) The correlation between ReHo and GScorr as being selective for rPM and pCC carries three major implications. Cross-scale desynchronization is not due to analysis biases related to a diffuse effect of the GS; in that scenario the ReHo-GScorr correlation should have been consistent for all the 7 regions (always present or always absent). This was not the case, though. The interdependence of local and local-to-global dysconnectivity appears to be selective for specific cross-scale pathways. This finding supports previous theories according to which associative areas such as rPM and pCC may have a deeper interaction with global brain activity (Yang et al., 2017). 4) As predicted, we found a moderate level of association between thought disorders and local-to-global correlation. 5) No GScorr alterations were found after GS regression, whereas ReHo reductions persisted unchanged. Also, when applying GS regression, ReHo and GScorr correlated in different regions (left-SensoryMotor and right-VisuoMotor, see Table S6) while correlations between symptoms and GScorr were canceled (Table S7). Together, these findings suggest that the global brain activity as operationalized by GS and GScorr carries important neurobiological and clinical information.

Incoherent experiences such as thought disorders may originate from failures in integration of information across different scales which may be put in relation by a "similar processing [which] pertains to all levels of the hierarchy" (Corlett and Fletcher, 2015). Our findings are in line with this model. In fact, they point out the presence of a cross-scale desynchronization within and between hierarchical levels; confirmation by future studies is needed.

https://doi.org/10.1016/j.schres.2021.02.021



B)
Local-to-global desynchronization

GScorr

	TYP		SCH		
	mean	SD	mean	SD	p
rPM	0.30	0.15	0.22	0.14	0.004**
lSM	0.28	0.14	0.22	0.14	0.012*
rVM	0.25	0.16	0.20	0.13	0.083
Cer	0.05	0.10	0.04	0.10	0.820
Tha	0.03	0.10	0.06	0.11	0.119
pCC	0.38	0.19	0.28	0.16	0.002**
aCC	0.32	0.19	0.23	0.18	0.013*

C)
Cross-scale desynchronization

ReHo-GScorr correlation

	TYP		SCH		All subjects	
	r	p	r	p	r	p
rPM	0.25	0.044*	0.41	0.003**	0.39	<0.001**
lSM	0.07	0.588	0.20	0.150	0.22	0.018
rVM	-0.08	0.512	-0.04	0.797	0.02	0.821
Cer	0.19	0.122	-0.18	0.214	0.04	0.634
Tha	-0.06	0.627	0.01	0.951	-0.09	0.344
pCC	0.31	0.011*	0.33	0.015*	0.39	<0.001**
aCC	0.11	0.369	0.14	0.315	0.21	0.023

D)
Psychopathology

Correlation to thought disorders

	ReHo				GScorr			
	Delusion		Conceptual disorganiz.		Delusion		Conceptual disorganiz.	
	rho	p	rho	p	rho	p	rho	p
rPM	-0.07	0.606	-0.21	0.127	-0.46	0.001**	-0.10	0.478
lSM	0.08	0.552	-0.10	0.504	-0.39	0.004**	-0.24	0.089
rVM	0.06	0.661	-0.16	0.274	-0.14	0.313	0.05	0.744
Cer	-0.27	0.058	-0.33	0.019*	-0.10	0.470	0.06	0.685
Tha	0.16	0.272	0.06	0.688	0.02	0.870	-0.01	0.963
pCC	-0.02	0.877	-0.25	0.073	-0.31	0.028*	-0.42	0.002**
aCC	-0.03	0.816	-0.11	0.442	-0.23	0.102	-0.14	0.323

rPM: right PreMotor; **lSM:** left SensoryMotor; **rVM:** right VisuoMotor; **Cer:** medial Cerebellum; **Tha:** bilateral Thalamus; **pCC:** posterior Cingulate; **aCC:** anterior Cingulate;
TYP: healthy neurotypical; SCH: schizophrenia; r: Pearson correlation coeff.; rho: Spearman correlation coeff.; SD: Standard Deviation; * uncorrected $p < 0.05$; ** Bonferroni corrected $p < 0.05$.

Fig. 1. A) Regions with reduced ReHo in both samples. B) Differences between TYP (n = 69) and SCH (n = 52) for GScorr C) Differences between TYP and SCH for ReHo-GScorr correlation. D) Correlation between neuronal and clinical measures in SCH group.

Funding

To GN, Michael Smith Foundation for Health Research, EJLB - Canadian Institute of Health Research, Canada Research Chair. To GN, National Natural Science Foundation of China (No. 31271195). To GN, Ministry of Science and Technology of China, National Key Research and Development Program of China (grant: 2016YFC1306700). To TJL, the Ministry of Science & Technology, Taiwan 105-2632-H-038-001-MY3, 108-2410–H-038-001 and 109-2410-H-038-009; the Ministry of Education, Republic of China (Taiwan) DP2-109-21121-01-N-07-01; the Taiwan Ministry of Health and Welfare IIT-1091-9; and the TMU Shuang Ho Hospital 109-TMU-SHH-23. To HLK and TJL, Taipei Medical University-Shuang Ho Hospital (103TMU—SHH—21).

CRediT authorship contribution statement

SD, original idea. SD, AS, and GN first draft. SD and AS statistical analyses. HLK and TJL, data collection. PP, HLK and TJL proof correction. PP and GN supervision.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

We deeply thank Dr. Niall Duncan for his support and proof-reading. Our thanks to Dr. Cheryl Aine and Dr. Margaret King for providing additional key data from the COBRE project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.02.021.

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25 June 2020
Available online xxxx