

MATTERS ARISING OPEN



Reply to: “Historical pursuits of the language pathway hypothesis of schizophrenia”

Lena Palaniyappan^{1,2}, Jingnan Du^{3,4,5}, Jie Zhang^{3,5}✉ and Jianfeng Feng^{3,5,6}✉REPLYING TO L.E. DeLisi *npj Schizophrenia* <https://doi.org/10.1038/s41537-021-00182-z> (2021)*npj Schizophrenia* (2021)7:54; <https://doi.org/10.1038/s41537-021-00183-y>

We appreciate the comments by Dr. DeLisi¹ regarding our study investigating the genetic determinants of language-network dysconnectivity in early-stage schizophrenia². In her comments, Dr. DeLisi highlights the missing historical context of the focus of our study and the lack of evidence linking our choice of language-related genes to the elevated genetic risk for schizophrenia. We concur with both of her observations and discuss how we can make further progress from the matters arising in this field of inquiry.

As pointed out by Dr. DeLisi, the three major contributions to our current thinking in the field of language and psychosis are Crow's theory on evolutionary origins, Chaika's linguistic exposition, and the large body of imaging work led by Dr. DeLisi. We fully agree that the association among language, schizophrenia and its genetics as proposed by Crow has been examined much earlier in several other works (see DeLisi et al.³ and other studies^{4–8}). More recently, a comparative connectomics study has established that schizophrenia-related dysconnectivity occurs in regions displaying human-specific connections not seen in chimpanzees⁹, adding support to Crow's notion that schizophrenia may be a price we pay for human evolution. Nevertheless, testing the genetic basis of the putative link between the *evolution of language* per se and the features of schizophrenia has been hitherto elusive. Thus, a direct association between genes that supposedly influence 'language-readiness' in humans and network-level dysconnectivity in schizophrenia remained unexamined prior to our study².

Dr. DeLisi cites several works that focussed on core language network as the substrate of the genetic risk of schizophrenia; in contrast, in our work we remained agnostic to the patterns of dysconnectivity that can be expected across the various stages of schizophrenia. In other words, we did not select the language regions a priori to study their dysconnectivity patterns; instead, we employed a “discovery” approach and conducted a brain-wide search. This agnostic stance comes from the large body of resting-state connectivity literature in schizophrenia and in genetic high-risk states where language networks have not emerged as the most affected modules (see Dong et al.¹⁰, Del Fabro et al.¹¹, and also Liloia et al.¹²). A purview of studies that specifically examine disruptions in overt linguistic aspects of schizophrenia (also called formal thought disorders), indicate that brain networks other than the core language network also play a crucial role in the clinical expression of schizophrenia¹³. There may be many methodological reasons for this observed lack of language-network primacy in fMRI literature that is beyond the scope of the current discussion. We believe some of the inconsistencies may indeed emerge from the effects of disease progression on the patterns of

dysconnectivity; separating patients with short and long duration of illness may provide more clarity. As a result, we undertook a whole-brain voxel-wise search to locate the spatial distribution of dysconnectivity separately in the short and long duration groups in a schizophrenia dataset consisting of 138 drug-naïve first-episode schizophrenia patients and 112 healthy controls^{2,14}. Our approach can reduce the false-positive rate and increase statistical power by appropriately utilizing the spatial information of fMRI data¹⁴. In our previous publications in collaboration with Crow, we have pursued the same brain-wide search approach^{15,16}, and demonstrated that patients with first-episode schizophrenia have functional dysconnectivity most prominently in the left inferior frontal gyrus (including Broca's area)¹⁵, and male patients in particular exhibit a predominantly left-lateralized pattern of aberrant connectivity with a focus on Broca's area¹⁶. Given the lack of a priori selection language networks in our study², we did not bring up the large body of fMRI and structural literature referred to by Dr. DeLisi that focuses on these networks.

In contrast to our lack of a priori selection of language-network seeds for the fMRI, we specifically chose a set of *language-readiness* genes for our pathway-specific polygenic risk scores. This was directly motivated by Crow's notion of linguistic primacy in schizophrenia and its connection with human evolution. Our selected candidate genes for language-readiness overlap with schizophrenia as well as brain development as listed by Murphy&Benitez-Burraco in their review¹⁷. The motivation for clustering these genes has been expounded in detail elsewhere^{18–20}. Our interest in FOXP2 was ignited by the various inherited and de novo variations in this gene noted in children with linguistic developmental disorders²¹ and the likelihood of its recent evolutionary selection (though this notion has come under scrutiny; see refs. ^{22,23}). We concur with Dr. DeLisi that “the genetics of schizophrenia remain elusive and is likely to be highly heterogeneous”. She is right to point out that FOXP2 pathway has not been implicated in large-scale studies seeking genome-wide associations or copy number variations as susceptibility markers for schizophrenia.

While the linguistic features of schizophrenia (often grouped as “formal thought disorders”) are notably familial, no single genetic pathway has been consistently associated with the linguistic readouts that typify this illness (see Nicodemus et al.²⁴ and Nestsiarovich et al.²⁵ for preliminary associations reported in this regard). It is possible that the genetic factors that influence linguistic features and the language-network architecture in schizophrenia are distinct from those that increase the susceptibility of schizophrenia per se. For example, subtle features of

¹Department of Psychiatry and Robarts Research Institute, University of Western Ontario, London, Ontario, Canada. ²Lawson Health Research Institute, London, Ontario, Canada.

³Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China. ⁴Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 200030 Shanghai, China. ⁵Key Laboratory of Computational Neuroscience and Brain Inspired Intelligence (Fudan University), Ministry of Education, Shanghai, China. ⁶Department of Computer Science, University of Warwick, Coventry CV4 7AL, UK. ✉email: jzhang080@gmail.com; jffeng@fudan.edu.cn

formal thought disorder can occur in otherwise healthy biological parents of patients²⁶. In Finnish Family Adoption studies, a family history of schizophrenia in biological parents did not confer an increased risk of formal thought disorders among the children living with adopted parents²⁷. On the other hand, the presence of schizophrenia increases the risk of subtle formal thought disorders among family members²⁸. Thus, we do not consider it necessary that a genetic pathway related to a specific feature such as functional dysconnectivity or formal thought disorder of schizophrenia should also relate to overall susceptibility to this complex polygenic illness. The fact that FOXP2 variations do not confer an elevated risk of schizophrenia, does not diminish the observation that its variations relate to the degree of dysconnectivity in the early stages of schizophrenia (for further discussion, see ref. ²⁹).

We and Dr. DeLisi agree on the notion of linguistic primacy in schizophrenia; we only differ in the roads we have chosen to travel. An impressively large body of work has tested if the genetic risk for schizophrenia primarily affects the language-network connectivity; in contrast, our modest work examined if the pattern of distributed dysconnectivity in the early stages of this illness relates to a specific genetic pathway of language readiness (FOXP2). Unlike the prior works cited by Dr. DeLisi, we do not test if the overall genetic susceptibility to schizophrenia converges on the language network per se. Instead, we report a possible genetic basis for the dysconnectivity of language-relevant regions early in this illness. The FOXP2 pathway does not appear to influence the pattern of dysconnectivity in the later stages of the illness, or the dysconnectivity of regions other than the left inferior frontal gyrus in the early stages. We recognize that the original paper, especially the content related to the language pathway hypothesis in our introduction, did not give a full overview of the valuable preceding work that led us here¹. Nevertheless, our choice of genetic targets centered on language-readiness remains close to Crow's original evolutionary notion of schizophrenia.

Our observation that a polygenic language-readiness pathway has a statistical association with Broca's area dysconnectivity in the early stages of schizophrenia, if replicated by others, may provide one piece of the puzzle that connects the evolution of language with schizophrenia. What value does the solution of this puzzle holds to the labyrinth of mechanistic origins of schizophrenia, is a matter that requires deeper consideration. We believe sustained multidisciplinary and international efforts are required to examine language in psychosis; in this regard, we support the new initiative 'DISCOURSE in Psychosis' (<https://discourseinpsychosis.org/>) that aims to tackle this in a collaborative manner.

DATA AVAILABILITY

The datasets generated during the current study are not publicly available due to ethical codes for this study but are available from the corresponding author on reasonable request with the approval of The Research Ethics Committee of the Shanghai Jiao Tong University School of Medicine.

CODE AVAILABILITY

No new codes were generated for this response. The BWAS: Voxel-level connectome-wide association studies code is publicly available at <https://github.com/weikanggong/BWAS>. The code used for the original study by Du et al. is publicly available at the following URL: <https://osf.io/zzaqv/>.

Received: 27 June 2021; Accepted: 13 September 2021;

Published online: 09 November 2021

REFERENCES

- DeLisi, L. E. Historical pursuits of the language pathway hypothesis of schizophrenia. <https://doi.org/10.1038/s41537-021-00183-y> (2021).
- Du, J. et al. The genetic determinants of language network dysconnectivity in drug-naïve early stage schizophrenia. *npj Schizophrenia* **7**, 18 (2021).
- DeLisi, L. E. Speech disorder in schizophrenia: review of the literature and exploration of its relation to the uniquely human capacity for language. *Schizophrenia Bull.* **27**, 481–496 (2001).
- Thermenos, H. W. et al. Altered language network activity in young people at familial high-risk for schizophrenia. *Schizophrenia Res.* **151**, 229–237 (2013).
- Sommer, I. E., Ramsey, N. F., Mandl, R. C., Van Oel, C. J. & Kahn, R. S. Language activation in monozygotic twins discordant for schizophrenia. *Br. J. Psychiatry* **184**, 128–135 (2004).
- Li, X. et al. An fMRI study of language processing in people at high genetic risk for schizophrenia. *Schizophrenia Res.* **91**, 62–72 (2007).
- Li, X. et al. fMRI study of language activation in schizophrenia, schizoaffective disorder and in individuals genetically at high risk. *Schizophrenia Res.* **96**, 14–24 (2007).
- Li, X. et al. Structural abnormalities in language circuits in genetic high-risk subjects and schizophrenia patients. *Psychiatry Res.: Neuroimaging* **201**, 182–189 (2012).
- Van Den Heuvel, M. P. et al. Evolutionary modifications in human brain connectivity associated with schizophrenia. *Brain* **142**, 3991–4002 (2019).
- Dong, D., Wang, Y., Chang, X., Luo, C. & Yao, D. Dysfunction of large-scale brain networks in schizophrenia: a meta-analysis of resting-state functional connectivity. *Schizophrenia Bull.* **44**, 168–181 (2018).
- Del Fabro, L. et al. Functional brain network dysfunctions in subjects at high-risk for psychosis: a meta-analysis of resting-state functional connectivity. *Neurosci. Biobehav. Rev.* **128**, 90–101 (2021).
- Liloia, D. et al. Updating and characterizing neuroanatomical markers in high-risk subjects, recently diagnosed and chronic patients with schizophrenia: a revised coordinate-based meta-analysis. *Neurosci. Biobehav. Rev.* **123**, 83–103 (2021).
- Sumner, P. J., Bell, I. H. & Rossell, S. L. A systematic review of task-based functional neuroimaging studies investigating language, semantic and executive processes in thought disorder. *Neurosci. Biobehav. Rev.* **94**, 59–75 (2018).
- Gong, W. et al. Statistical testing and power analysis for brain-wide association study. *Med. image Anal.* **47**, 15–30 (2018).
- Li, T. et al. Brain-wide analysis of functional connectivity in first-episode and chronic stages of schizophrenia. *Schizophr. Bull.* **43**, 436–448 (2017).
- Wang, Q. et al. "Brain connectivity deviates by sex and hemisphere in the first episode of schizophrenia"—a route to the genetic basis of language and psychosis? *Schizophrenia Bull.* **45**, 484–494 (2019).
- Murphy, E. & Benítez-Burraco, A. Bridging the gap between genes and language deficits in schizophrenia: an oscillopathic approach. *Front. Hum. Neurosci.* **10**, 422 (2016).
- Boeckx, C. & Benítez-Burraco, A. Globularity and language-readiness: generating new predictions by expanding the set of genes of interest. *Front. Psychol.* **5**, 1324 (2014).
- Boeckx, C. A. & Benítez-Burraco, A. The shape of the human language-ready brain. *Front. Psychol.* **5**, 282 (2014).
- Benítez-Burraco, A. & Boeckx, C. Possible functional links among brain-and skull-related genes selected in modern humans. *Front. Psychol.* **6**, 794 (2015).
- Den Hoed, J. & Fisher, S. E. Genetic pathways involved in human speech disorders. *Curr. Opin. Genet. Dev.* **65**, 103–111 (2020).
- Atkinson, E. G. et al. No evidence for recent selection at FOXP2 among diverse human populations. *Cell* **174**, 1424–1435. e1415 (2018).
- Fisher, S. E. Human genetics: the evolving story of FOXP2. *Curr. Biol.* **29**, R65–R67 (2019).
- Nicodemus, K. K. et al. Category fluency, latent semantic analysis and schizophrenia: a candidate gene approach. *Cortex* **55**, 182–191 (2014).
- Nestsiarovich, A. et al. Disorganization at the stage of schizophrenia clinical outcome: clinical-biological study. *Eur. Psychiatry* **42**, 44–48 (2017).
- Goldstein, M. J. et al. Family interaction versus individual psychopathology. *Br. J. Psychiatry* **161**, 97–102 (1992).
- Roisko, R., Wahlberg, K.-E., Hakko, H. & Tienari, P. Association of adoptive child's thought disorders and schizophrenia spectrum disorders with their genetic liability for schizophrenia spectrum disorders, season of birth and parental communication deviance. *Psychiatry Res.* **226**, 434–440 (2015).
- Subotnik, K. L., Goldstein, M. J., Nuechterlein, K. H., Woo, S. M. & Mintz, J. Are communication deviance and expressed emotion related to family history of psychiatric disorders in schizophrenia? *Schizophrenia Bull.* **28**, 719–729 (2002).
- Palaniyappan, L. Dissecting the neurobiology of linguistic disorganisation and impoverishment in schizophrenia. *Seminars in Cell & Developmental Biology*. <https://doi.org/10.1016/j.semdb.2021.08.015> (2021).

ACKNOWLEDGEMENTS

This work was supported by Shanghai Municipal Science and Technology Major Project (No. 2018SHZDX01) and J.Z. Lab (to J.Z.); NSFC 61973086 (to J.Z.); Shanghai

Science & Technology Innovation Plan key project grant nos. 15JC1400101 and 16JC1420402 (to J.F.); National Natural Science Foundation of China grant nos. 71661167002 (to J.F.), 91630314 (to J.F.); Shanghai AI Platform for Diagnosis and Treatment of Brain Diseases grant no. 2016-17 (to J.F.); Base for Introducing Talents of Discipline to Universities grant no. B18015 (to J.F.); L.P. was partly supported by Canadian Institute of Health Research Foundation Grant (grant number 375104); Opportunities fund and Innovation fund for Academic Medical Organization of Southwest Ontario; Bucke Family Fund, The Chrysalis Foundation and The Arcangelo Rea Family Foundation (London, Ontario). L.P. acknowledges salary support from the Tanna Schulich Chair of Neuroscience and Mental Health.

AUTHOR CONTRIBUTIONS

L.P. and J.D. wrote a first draft of the paper. J.Z. and J.F. provided feedback throughout the work and contributed to the writing of the response.

COMPETING INTERESTS

L.P. reports personal fees from Otsuka Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Sunovion and Otsuka Canada outside the submitted work. L.P. is the convenor of DISCOURSE in the Psychosis consortium. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Jie Zhang or Jianfeng Feng.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2021