April 15th, 2024

Dear Dr. Krystal,

Please consider our manuscript, entitled “Multivariate Association between Functional Connectivity Gradients and Cognition in Schizophrenia Spectrum Disorders” for consideration as an Archival Report in *Biological Psychiatry*.

Schizophrenia spectrum disorders (SSDs) are characterized by cognitive deficits relating to dysconnectivity between unimodal and multimodal networks. However, little is known regarding how such connectivity relates to social and non-social cognitive performance specifically in SSDs, and how such brain-behavior relationship contributes to the daily life of participants with SSDs. We used harmonized data from the National Institute of Mental Health (NIMH)-funded “Social Processes Initiative in the Neurobiology of Schizophrenia(s) (SPINS)” multicenter study, where multimodal data were collected from 185 healthy controls and 301 participants with SSDs. We first extracted principal gradients from resting-state connectivity data to characterize their functional network organization and used partial least squares correlation (PLSC) to examine its multivariate association with both social and non-social cognitive performance. We then examined the clinical relevance of such brain-behavior relationships by examining the correlation between the identified PLSC dimension and clinical and functioning outcomes of participants with SSDs.

Our results showed that participants with SSDs featured less network segregation along the unimodal-multimodal gradient, the visual-sensorimotor gradient, and the default-frontoparietal gradient. Such segregations were associated with social and non-social cognition, and these associations were shown clinically meaningful as they correlated with participants symptoms, quality of life, and functioning in SSDs. We believe this study holds relevance for the diverse readership of *Biological Psychiatry*, offering insights into the nature and mechanisms of psychiatric disorders by illuminating potential prognostic markers associated with SSDs.

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I affirm that this manuscript is an original, unpublished study that has not been submitted for simultaneous consideration by any other journal. The authors have no potential conflicts of interest to disclose.

Sincerely,

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