Dear Editor,

We are pleased to present our manuscript, “Test-retest reliability of functional connectivity in depressed adolescents”, to be considered for publication in *Biological Psychiatry.*

Biomarkers derived from rsfMRI could aid clinicians in diagnosing and predicting psychiatric illness and guide individualized treatment protocols, a concept broadly known as “precision medicine”. However, rsfMRI research has been challenged by concerns over its test-retest reliability—the stability of repeated measures. Low test-retest reliability limits the observable effect size of an association between measures, reducing the power to identify reproducible biomarkers. Previous investigations have found poor reliability of rsfMRI functional connectivity, which may contribute to the small effect sizes of brain-behavior associations. However, these studies have primarily taken place in healthy adult populations and measured univariate reliability (assessing one connection at a time). Thus, reliability in more clinically relevant populations – such as those with psychiatric illness, or in a developmental stage – remains to be established. Furthermore, the field has increasingly focused on multivariate approaches using machine learning or other more complex models with parameters from the entire connectome. It is important to inform these methods by assessing multivariate reliability in addition to univariate.

We compared the longitudinal test-retest reliability of resting-state fMRI (rsfMRI) functional connectivity in healthy adolescents and adolescents with major depressive disorder. We found little evidence for an association between reliability and depression. Furthermore, while both groups had poor univariate reliability, we observed excellent multivariate reliability across the 1-year interval between scans.

Our results have implications for anyone interested in the potential for neuroimaging to facilitate precision psychiatry. Through a comprehensive understanding of the reliability of rsfMRI functional connectivity in depressed adolescents, we can inform future investigations of biomarkers of mood disorders. Our results suggest that multivariate analyses in depressed and healthy populations may provide greater power to detect reproducible effects.

We believe our findings will be of substantial interest to the general readership of *Biological Psychiatry*. This work is not under review elsewhere, and we have no conflicts of interest to disclose. We would be happy to answer any further questions you may have; please address any correspondence to [chris.camp@yale.edu](mailto:chris.camp@yale.edu). Thank you for considering our manuscript for publication in *Biological Psychiatry*.

Sincerely,



Dylan Nielson, Ph.D. Chris Camp, B.S.