*Biological Psychiatry*  
MS Number: BPS-D-24-00589   
Title: Multivariate Association between Functional Connectivity Gradients and Cognition in Schizophrenia Spectrum Disorders   
  
Dear Dr. Ju-Chi Yu,  
  
Thank you for submitting your work to *Biological Psychiatry*. It has been reviewed by experts in the field, and their comments are enclosed. Although well received, this manuscript did not make the final cut for a revision due to the presence of several even stronger papers that are being evaluated simultaneously by the Editors. I realize that this is disappointing news. In many cases such as this, we understand that you would likely be able to address many of the reviewers' concerns. Unfortunately, limited journal space and a large number of submissions require us to reject over 90% of all submitted papers. As a result, we often are forced to make difficult decisions and reject manuscripts with considerable merit.  
  
However, precisely because of the high quality of this paper and after discussion with the editorial team, I would like to extend an offer to you that this paper be revised and transferred to *Biological Psychiatry*'s sibling journal, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (BP:CNNI), for further consideration. BP:CNNI is a premier venue for research in cognitive neuroscience and neuroimaging. It is indexed in MEDLINE/PubMed and is also included in Clarivate's *Journal Citation Reports*, which includes the Impact Factor and other metrics.  
  
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If you would like to take advantage of this transfer opportunity, you will be expected to revise your paper, taking into account the peer reviewers' comments, and to also prepare and include a response to reviewers. Upon acceptance of the transfer offer, we will establish a one month due date for revision of the article.  
  
Please note that this offer does not constitute a guarantee of acceptance at BP:CNNI, but it is our hope that the transfer option will help expedite the evaluation process for this promising paper. Our article transfer service removes the need to complete the entire submission process again, saving you valuable time and effort by transferring your manuscript files and details regarding the peer review process. Note that you may already have an author account at BP:CNNI and if so, should not sign up for a new one to complete the transfer process.  
  
If you do not wish to transfer your paper, *Biological Psychiatry* is a member of the Neuroscience Peer Review Consortium (NPRC), an alliance of neuroscience journals that have agreed to share manuscript reviews with each other. At your request, we can forward the reviews of your manuscript if you submit to another NPRC journal. You can find a list of Consortium journals and details about forwarding reviews at nprc.incf.org.  
  
I hope the reviewers' comments are helpful to you as you revise the paper. I am sorry the decision was not more positive and hope it does not discourage you from submitting new work to *Biological Psychiatry* in the future.  
  
For your guidance, the reviewers' comments are included below. We hope you will be interested in allowing us to consider this submission for publication at BP:CNNI, but otherwise wish you success in finding a home for this interesting work. Thank you for giving us the opportunity to consider your article.  
  
Yours sincerely,   
  
Dr. John H. Krystal   
Editor   
*Biological Psychiatry*

**Reviewer Comments:**  
  
**Reviewer 1:** Comments to authors:  
  
Thank you for the opportunity to review "Multivariate Association between Functional Connectivity Gradients and Cognition in Schizophrenia Spectrum Disorders" by Yu and colleagues. The manuscript describes a functional imaging study looking at the relationship between connectivity and clinical symptoms in schizophrenia symptom disorders. The authors use connectivity gradients as a frame of reference and relate individual differences in gradient positions to individual differences in cognitive scores. The study asks an interesting question, but as I outline below, the methods are indirect and it is unclear what biological inferences can be made from them.  
  
(1) The main obstacle is the transformation to gradient space. I understand that this is a popular method in the literature, but the drawbacks are evident here. Namely, the results of the analysis are that some regions climb up or down in these putative hierarchies, and that that this is related to individual differences in cognition. Are these changes related to anatomical connectivity? Are they related to changes in intracortical myelin, as the authors posit? At the end of the paper, I was not sure what the main result was, and this is an inherent problem in these studies that seek to identify gradient "compression" or "expansion". Why not just focus on the original functional connections that at least have some direct correspondence with the feature studied (connectivity)?

Maybe checking the intracortical myelination or clarify in the discussion  
  
(2) Please cross-validate the PLS model. As the authors are probably aware, these models tend to overfit and permutation tests on their own do not provide enough evidence that the model would generalize.

Run PLS cross validation  
  
(3) Why go back to Pearson correlations after ComBat? Why not just stay with the Z-transformed values?

Confirm that this is true and is what we did - Explain that this is what the gradient function asks for

(4) Gradients were aligned to some template via Procrustes rotation. What was this template? Also, how good was the alignment?

Mention Margulies’s results and add to the method section. Check the alignment – compare to Margulies’s map  
  
  
**Reviewer 2:** Comments to authors: In this manuscript Qi et al. take the approach of Marguiles et al. (PNAS 2016) i.e. a framework in which the functional connectivity of the brain can be organized around two (or three) axes with one axis being a visual vs somatomotor gradient and the other being a unimodal versus heteromodal ("sensation vs cognition") gradient. This organization scheme is observed across multiple datasets and even extends to NHPs. Dong et al 2021 demonstrated that these gradients exist in individuals with schizophrenia as expected, but the topology of these gradients is altered: specifically with a compression of gradients such that the range of values in the visual-somatomotor range is shifted away from the most extreme values. Wang et al. 2020 replicated this result and further linked regional hotspots of this compression to a variety of cognitive/clinical factors. Here Qi et al apply this approach to a novel dataset of individuals with schizophrenia spectrum disorders collected at multiple sites with a particular emphasis on social cognitive ability.  
  
Qi et al. are (reassuringly) able to replicate the gradient compression observed by Dong et al. and Wang et al. Furthermore, they do a wonderful job of visualizing the contributions of individual components to the overall compression pattern observed in these studies. Additionally, a multivariate analysis (PLSC) between cognitive performance and clinical symptoms is presented.  
  
Strengths of this paper include the relatively large sample size, careful cognitive characterization of the participants, beautifully informative visual representation of results, and thoroughly described imaging methods. As a fan of publishing replication studies, I'm particularly excited to see that the results of Dong and Wang are being replicated here.  
  
Because these results replicate (and extend) those prior findings, my only concerns are two methodological questions that are shared across all of these papers:  
  
First, I noted that the only motion exclusion was removing 5 (of over 400) participants for excessive motion e.g. mean FD > .05. The mean FD for each group is strikingly low and that's truly admirable for a multi-site study, especially in this population. At the preprocessing stage I don't see any correction for the contribution of micro movements in the FD<.05 range. We do know that these movements directly impact measured functional connectivity (e.g. Power et al 2012) and group comparisons between clinical and typically developing populations are most vulnerable to this kind of confound. Rather than suggest which method of motion correction should be used, I'd like to see visualization of the effects of motion on the gradients described i.e., if one does a median split within-groups e.g. comparing top-half movers to bottom-half movers of individuals with SSD or top-half to bottom-half movers of HC individuals and you map out the trajectories of gradients as in Figure 2, is there movement of the gradient in a direction? Showing that high movement doesn't result in SM->Vis compression would be reassuring.

Check results with the medain-FD split  
  
Second, the analysis showing that the visual->somatomotor axis is compressed is predicated on the idea that the glasser atlas and cole-anticevic brain network parcellation derived from control populations maps accurately onto individuals with SSD. Given the recent suggestion that clinical populations may have differences/expansions of network topography ([https://www.biorxiv.org/content/10.1101/2023.08.09.551651v1.full](https://urldefense.com/v3/__https:/www.biorxiv.org/content/10.1101/2023.08.09.551651v1.full__;!!FxkXuJIC!fJ6mNeavtsbtty1hJUfjtBKGGxY5eYtXp-dcd42PXE961IoffhrW_nGjAh9wxnBNOeGW1C3XWiQtP2E1BQ$)) how can we determine if the "compression" observed and replicated across studies is not in fact simply an artifact of brain networks in SSD not mapping neatly onto parcels derived from healthy control participants? Is there a brain parcellation that is analogous to the Glasser atlas but derived from SSD participants that could be used instead?

Check for SSD atlas, but mention that this is a valid point, but we do not have enough data to derive individualized parcellation for our group.  
  
Small question for the discussion section: Did the major contributors to group differences (in Figure 2) and the cognitive correlations (Table 2) match with prior published results by Dong et al and Wang et al?  
  
Confirm correlation results  
  
**Reviewer 3:** Comments to authors:  
The submitted study concerns associations between cognitive dysfunction and a relatively new metric regarding brain connectivity in schizophrenia patients. Results contain some interesting aspects, but several issues must be addressed before a potential decision regarding the manuscript  
- Considering a huge amount of connectivity studies in schizophrenia, and numerous indicators regarding neural network organization, authors should present specific arguments informing why they consider the results of the principal gradient analysis as a better index compared with others. Unfortunately, the increasing number of connectivity-focused algorithms has not ultimately translated into significant progress in understanding brain dysfunction in mental illness.  
- "Principal gradients also account for geodesic features between  
brain regions - i.e., given the assumption that two closer brain regions are more likely to be functionally connected: (pp. 8) - was this assumption empirically confirmed? If so, a reference should be added.

Clarify, reword, and add reference

- What exactly means gradient-dependent differentiation regarding networks? If the authors' write: "Specifically, on Gradient 1 (unimodal vs. multimodal), somatomotor (SMN), primary and secondary visual (VIS1 and VIS2), and default mode networks (DMN) are found to be less differentiated from auditory (AUD), cingulo-opercular (CON), frontoparietal (FPN), and subcortical (SUB) networks in participants with SSDs than in Controls, q<.05.", does it mean that when regions belonging to VIS1 activate, then also regions from DMN activate? If so, does it just mean that the connectivity between the perception network and the off-task network is too high? Elaborate in detail and refer to already well-known indexes or explain in more detail what newly presented gradient results suggest.

Elaborate and clarify in the intro or method section, then reword and clarify in the results section

- Were the correlations between the network gradient results and the dose of antipsychotic drugs in the patient group checked?

Check if gradient compression relates to CPZ-equivalence

- What other psychotropic drugs apart from antipsychotics were taken by patients with schizophrenia spectrum?

Add to the method section

- Since the clinical group is a psychotic spectrum, what exactly was the percentage of specific diagnoses in it?

Provide more detailed diagnosis information; compute percentages

- Unfortunately, there is no data on the duration of the disease, the number of hospitalizations, the period of untreated psychosis, and other clinical variables regarding the course of the disease that could have influenced the obtained results.

- The results regarding the relationship between network gradients and cognitive function could have been better presented if three 'sets' of results were shown: 1) in the SSD group only, in the HC group only, and 3) in the combined groups. Such a comparison would clearly show whether there are typical relationships specific to the schizophrenia spectrum, or whether network data simply correlate with cognitive functioning in a way that is not specific to a specific clinical group.

Add PLSC for specific groups

- The results indicating that altered compression patterns involving sensory networks significantly explained the generalized cognitive deficit in schizophrenia are the most interesting and, in my opinion, the most valuable finding of this study. This is somewhat at odds with a significant number of results showing a relationship between cognitive function and large-scale task networks such as the FPN or CEN.

Addressed in the discussion, but can be emphasized and explained more  
  
And in the end, the most important problem: schizophrenia is already a well-known disconnection disorder. So, it is quite easy to expect that a comparison between such a clinical group and control group regarding neural network organization will bring significant differences. On the other hand, since cognitive dysfunction in schizophrenia are also very well presented, it is also quite easy to obtain correlations between network measures and cognitive indexes. So, the general results of this study are possible to predict even without empirical testing. Of course, such predictability does not concern details, but again, the details are heterogenous.

Emphasize in the discussion: The merit of the study is to be able to identify correlations with specific networks and cognition, especially including multiple aspects of social cognitions. It is also worth knowing that the brain-behavioral relationships still relate to the clinical outcomes even when the participants are under treatment and are stable.  
  
  
**Reviewer 4:** Comments to authors:  
In this manuscript, Yu et al. examined relationships between functional connectivity gradients and cognition in a fairly large sample of people with schizophrenia spectrum disorders (SSD). They identified 3 such gradients, each of which was less differentiated in SSD than in controls. Moreover, the first gradient was positively correlated with negative symptoms and functioning in the patient group. The manuscript covers important work and is well done, with some of the methods being developed by co-authors. In addition, they do a good job comparing their results to those for other diagnoses. The paper is also well written. However, I do have a number of concerns.  
  
First, the Abstract should include the final sample rather than the sample they started with. In the Results section, they state that they ended up with 248 people with SSD and 172 controls. As a related point, they should examine whether excluded participants differed in any systematic way from those who were retained.

Correct in the method section; check if there is any systematic removal  
  
Second, in the Introduction (lines 32-33), the authors state that "decreased segregation is represented by networks moving toward the center from both ends of the gradient axes . . ." It should be clarified whether they mean this in a mathematical sense (e.g., less broad distribution of scores) or spatially (reduced spatial distribution of the gradients), or something else.

Clarify and reword in the introduction  
  
Third, in the paragraph on Social and non-social cognition in SSD, the authors cite their own work, but there is a very extensive literature on such deficits in SSD, and they should cite some of that.

Add references for Social vs. non-social cognition in SSD  
  
In the Methods section, the MRI resting sequence is fairly short (7 minutes). This should be added to the section on Limitations (which should be denoted as such in the Discussion). Moreover, participants had their eyes closed during the scan. Was wakefulness verified in any way?

Check and add to discussion (verify wakefulness?)  
  
Also in the Methods, I note that global signal was used as a nuisance regressor. There has been a long standing controversy about whether this induces negative FC, as well as whether the signal is heterogeneously distributed across the brain. They should justify their use of the regressor and/or include it in the Limitations section.

Justify the regression of global signal  
  
The Results are very interesting, as I said earlier, but I found some of them to be counterintuitive. For example, in the legend for Figure 1A, the authors state that "Warm colors indicate SSDs being significantly closer to, respectively, for each gradient, the frontoparietal, the vision, or the frontoparietal networks than Controls." The Figure itself says the comparison is Controls > SSD, which would suggest just the opposite. The authors should clarify for the reader what the plotted data actually mean (i.e., do higher scores mean more less differentiated networks, which would be counterintuitive, or do they mean closer to one part or the other part of the gradient as seems more likely?). Similarly, on line 23 of the 2nd page of the results, the authors state that "On Gradient 2, the identified ROIs within DMN were those medial regions closer to FPN and temporal regions closer to VIS." What does closer mean in this context? Less different, or literally physically closer? In general, the meaning of gradient scores should be made clearer, as should how they lead to interpretations of network differentiation between groups.

Clarify in the intro and method; check and maybe regenerate the graph  
  
In the Discussion, the authors should cite some of the broad literature by other groups showing sensory abnormalities in SSD in addition to their own work.  
Add references to discussion  
Minor points:  
One line 43 of the Discussion, the authors should state in whom increased thalamic-sensory connectivity is shown, as it indicates a comparison.  
  
In general, "increased" and "decreased" should be avoided unless the data are longitudinal. Preferred terms are "higher" and "lower."