Gmail **Brian Pho <brianpho7@gmail.com>**

Fwd: Decision on submission to Developmental Cognitive Neuroscience

7 messages

Bobby Stojanoski <bobby.stojanoski@gmail.com> Mon, Mar 4, 2024 at 7:34 PM
To: Brian Pho <brianpho7@gmail.com>, Yalda Mohsenzadeh <ymohsenz@uwo.ca>, Ryan Stevenson <ryan.andrew.stevenson@gmail.com>

Hello!
We got reviews back from Developmental Cognitive Neuroscience. It's an R&R which I think is good news. I haven't gone through the reviews in detail, but at first glance they seem fair and not too harsh, although there are a couple of points that will require a bit of work.
I'll start working on the response letter and I'll send you that and the updated manuscript in a few weeks. If you have ideas/suggestions for responding to the reviewer points, please let me know.

Best,
Bobby

---------- Forwarded message ---------
From: **Developmental Cognitive Neuroscience** <em@editorialmanager.com>
Date: Fri, Mar 1, 2024 at 2:42 PM
Subject: Decision on submission to Developmental Cognitive Neuroscience
To: Bobby Stojanoski <bobby.stojanoski@gmail.com>

Manuscript Number: **DCN-D-24-00015**

Identifying Developmental Changes in Functional Brain Connectivity Associated with Cognitive Functioning in Children and Adolescents with ADHD

Dear Dr Stojanoski,

Thank you for submitting your manuscript to Developmental Cognitive Neuroscience.

I have completed my evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following major revision. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by **Mar 22, 2024**.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed.

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Developmental Cognitive Neuroscience values your contribution and I look forward to receiving your revised manuscript.

Kind regards,
Sarah Whittle
Editor

Developmental Cognitive Neuroscience

Editor and Reviewer comments:

Reviewer #1: Pho and colleagues used movie-watching functional connectivity to study individual differences in cognition in typically developing youth and youth with ADHD. Overall, I enjoy reading the manuscript as I like authors' clear and creative usage of data-driven methods. The authors split participants into three age bins, i.e., early childhood (Bin 1: ages 6-8, n=114), middle childhood (Bin 2: ages 9-11, n=147), and adolescence (Bin 3: ages 12-16, n=112), and evaluated age-specific models to predict cognitive measures, with the goal to test whether the same set of cognitive measures can be predicted across different development stages. Three caveats undermine the credibility of the conclusion: 1) age bins have different age ranges (3 years for bin 1 and 2, 5 years for bin 3) which may translate to more heterogeneity in bin 3, and 2) different numbers of subjects per age bin which will affect prediction performance; 3) it is not clear whether there are any other systematic differences across groups (e.g., gender/motion/cognitive measures/ADHD subtypes/symptom scores). My detailed comments can be found below.
1."By splitting participants into three age bins, the models would either 1) predict the same set of cognitive abilities for all three age bins, suggesting a similar functional connectivity profile across development or 2) predict a different set of cognitive abilities for each age bin, suggesting the model captured a functional connectivity profile unique to age cohorts." This is the key claim, however, I wonder if any other factors, such as sampling variability, can influence how well cognitive abilities can be predicted. Authors can test it empirically by randomly splitting the entire dataset into 3 groups repeatedly (n = 114, 147, and 112) and test the predictive performance. If the predictability is specific to age bins, we would see randomly splitting data consistently lead to worse performance than age-constraint data. Ideally, the predictive performance of 95% models using randomly split data is worse than that of age-constraint models (at least for bin 1 and 2).

2.Along similar lines, an alternative explanation for failure of the bin 3 model is the larger age range. I wonder what predictive performance is if authors randomly sample 112 subjects between say 7-11 years old and rerun the analysis to see the predictive performance still remains significant.

3.Related to earlier comment, "Conversely, we could not predict FSIQ (r=0.04, p=.42) … in the NT group (n=106)." How much of it is caused by the lower N and/or much larger age span? Authors could repeat the analysis with the n=106 ADHD participants across the entire age range motion matched with NT group, to enable a fair comparison. If ADHD group also fails, then then the alternative conclusion is more plausible.

4.Are there any group differences, such as cognitive measures and symptom scores, across three age groups? What is predictive performance for each age bin in the combined model as shown in Table 2? Can any correlation be driven by age or motion? Authors can run a partial correlation between predicted and true outcomes, partialling out age, motion among other nuisance factors?

5.The multiple comparison is corrected with max-statistic method (Nichols & Hayasaka, 2003). I am not familiar with the method and cannot find the citation either. The closest one that I can find is "Hayasaka, Satoru, and Thomas E. Nichols. "Validating cluster size inference: random field and permutation methods." Neuroimage 20.4 (2003): 2343-2356," which uses permutation tests to determine a null cluster size to control for multiple comparisons for activation studies. I am not sure if the method is appropriate here. Authors can consider switching to more conventional methods like FDR. Are all p values corrected from permutation tests?

6.It is interesting that authors claim that "Emerging from our results was predicting higher-level cognitive abilities followed an inverted-U pattern," however, I would argue this might be an overextrapolation given the merely three age bins which are not well-motivated to begin with. To systematically verify the claim, authors can sample the equal number of subjects per three-years interval from 6 to 16, and build the predictive models across age bins (6-8, 7-9, 8-10, etc.), and plot model performance as a function of age bins. The fact that the models translate across age bins, contrary to authors' hypothesis, indicates that those age bins may or may not be the deciding factor.

Minor:
In the abstract, authors stated "We applied machine learning models to identify patterns of network connectivity …, our models successfully predicted IQ, visual spatial, verbal comprehension, and fluid reasoning in children, but not in adolescents with ADHD". May want to specify the age range of children and adolescents here.

It is fine to report r squared and/or r, but authors may want to be consistent. Also, as noted by authors, "using Ridge regression, we predicted the age (r2=0.45, p=.01) and sex of individuals in the ADHD group (n=373)," p =0.01 seems to

be a bit large for a r squared of 0.45.

When authors described the overall models, i.e., "Across all cognitive measures, models consistently assigned the largest positive weights to connections within two networks: memory retrieval and sensory/somatomotor (mouth)…" authors can include a heat map showing the frequency.

Are all cognitive measures age-normed?

Reviewer #2: In this work, the authors apply Ridge and PLS to the HBN dataset to find functional brain connectivity associations with individual differences in dimensions of WISC within an ADHD sample spanning 6 to 16 years of age. The use of naturalistic fMRI data (video watching) for this purpose is a strength of the study. Below are my concerns/suggestions:

Abstract

-I don't think the conclusion "This work demonstrated that computational models applied to neuroimaging data in response to naturalistic stimuli can identify distinct neural mechanisms associated with cognitive abilities at different developmental stages in children and adolescents with ADHD." Is valid based on the methods and results. Specifically, neural correlates are tested not mechanisms. I would also say machine learning or multivariate models instead of computational models to be more specific and also because that term is usually used for computational modelling studies (e.g. diffusion models, reinforcement learning models, etc.).

-I would also include the N for the ADHD sample.

Introduction

Paragraph 2: Second sentence says 'recent' studies but cites work from 2003, 2006, and 2015. Also this study is about functional connectivity but the work related to ADHD that are cited are based on fMRI activity. I suggest adding more recent and relevant work in this paragraph and the next one.

Paragraph 3: Considering this is not a longitudinal study, but just a cohort with wide range of ages, I suggest tempering the sentences on the research gaps that are being addressed here.

Paragraph 4: Introducing functional brain connectivity and large body of work using connectivity to predict cognitive processes such as attention among children with ADHD is needed here.

Methods

-The sample sizes within each age bin are not large enough to produce reliable feature weights, therefore we can't be sure if differences found between age bins are due to unreliability of features or meaningful developmental differences. If the authors can do a split-half ICC analysis for each age bin and show the models trained on two halves of the same age bin are significantly more similar than models across age bins, and report those ICC values, we can determine if the results are interpretable in a developmentally meaningful way or not.
Results

- Not utilizing the NT participants to ground the age-specific findings in the ADHD children makes it very difficult for me to interpret any of the reported results.

-In figure 3, some of the r's on the main diagonals are smaller than off-diagonal r's. This is concerning and shows that models are not really benefitting at all from the age binning.

Discussion

- I couldn't follow the inverted-U argument.

Limitations:

-Some of the points can potentially be evaluated if there is information about participants level of engagement with the video clip and whether they had seen it before etc.

Minor:
-In the Tables the label used for NT is written as TD please be consistent.
-in the section 'cross-prediction across age bins in ADHD' the last sentence of the first paragraph has an extra 'to' at the end.

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Brian Pho <brianpho7@gmail.com> Wed, Mar 13, 2024 at 2:48 PM
To: Bobby Stojanoski <bobby.stojanoski@gmail.com>

Meeting Notes

Reviewer 1
1. In response to age bin thresholds and bin size: " Furthermore, Baum and colleagues found that the trajectory of executive performance develops rapidly between the ages of 8 to 14 but plateaus from age 14 to 22" page 3 thesis.
2. Merge bins 1 and 2, and resample.
5. Max-stat vs FDR: https://github.com/Brian-Pho/MSc_Research-Project/blob/main/src/Analysis/Multiple%20Hypothesis%20Testing%20Correction.ipynb

Reviewer 2
1. ICC results: https://github.com/Brian-Pho/MSc_Research-Project/wiki/Final-Results#between-age-bin
2. NT age bin results: https://github.com/Brian-Pho/MSc_Research-Project/wiki/Other-Results#healthy-age-bins-n106
3. Cross prediction why the off-diagonal has better prediction than on-diagonal: " I also found the reverse pattern—a model trained on Bin 2 and tested on Bin 1—can successfully predict FSIQ (r=0.36, p=.002), VSI (r=0.40, p=.002), VCI (r=0.30, p=.002), and FRI (r=0.20, p=.01). This was surprising because I had hypothesized that the models would extract unique network patterns for each age bin, and that those unique patterns would not generalize to other developmental stages. Instead, the ability to cross-predict FSIQ, VSI, VCI, and FRI from Bin 1 to Bin 2, and from Bin 2 to Bin 1, suggests that the models extracted similar, generalizable network" page 35-36 thesis.

[Quoted text hidden]

Bobby Stojanoski <bobby.stojanoski@gmail.com> Fri, Mar 22, 2024 at 8:38 AM
To: Brian Pho <brianpho7@gmail.com>

Hey Brian,
Have you had a chance to run those analyses? Do you want to meet early next week?

Best,
Bobby
[Quoted text hidden]

Brian Pho <brianpho7@gmail.com> Sat, Mar 23, 2024 at 12:50 PM
To: Bobby Stojanoski <bobby.stojanoski@gmail.com>

Hey Bobby,

I haven't had a chance to run the analyses so next week is too soon. I'll try to run them in the next week.

Thanks,
Brian
[Quoted text hidden]

Bobby Stojanoski <bobby.stojanoski@gmail.com> Mon, Mar 25, 2024 at 11:45 AM
To: Brian Pho <brianpho7@gmail.com>

Hey Brian,
Sounds good.
Do you want to meet on Tuesday next week?

Best,
Bobby
[Quoted text hidden]

Brian Pho <brianpho7@gmail.com> Tue, Apr 2, 2024 at 12:34 AM
To: Bobby Stojanoski <bobby.stojanoski@gmail.com>

Hey Bobby,

I can't meet this Tuesday because I have a job interview. I'll let you know when I've completed the analysis.

Thanks,
Brian
[Quoted text hidden]

Bobby Stojanoski <bobby.stojanoski@gmail.com> Wed, Apr 3, 2024 at 2:00 PM
To: Brian Pho <brianpho7@gmail.com>

Hey Brian,
No worries. How did your interview go?
I spoke to the journal and they granted us an extension until the 15th.

Can we meet early to mid next week?

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