Editor:

Thank you again for submitting your manuscript "Mapping the spatiotemporal continuum of structural connectivity development across the human connectome in youth" to Nature Communications. We have now received reports from 3 reviewers and, after careful consideration, we have decided to invite a major revision of the manuscript.

As you will see from the reports copied below, the reviewers raise important concerns. We find that these concerns limit the strength of the study, and therefore we ask you to address them with additional work. Without substantial revisions, we will be unlikely to send the paper back to review.

If you feel that you are able to comprehensively address the reviewers' concerns, please provide a point-by-point response to these comments along with your revision. In this response, please reference line numbers in the manuscript where changes have been made and/or reproduce the changes in the response letter. Please also show all changes in the manuscript text file with colour highlighting. If you are unable to address specific reviewer requests or find any points invalid, please explain why in the point-by-point response.

Reviewer #1 (Remarks to the Author):

This study by Xu et al. shows an impressive investigation into the spatiotemporal development of structural connectivity (SC) across childhood and adolescence. By leveraging three independent, large-scale datasets (HCP-D, ABCD, and the Chinese youth), the authors map the spatiotemporal dynamics of white matter maturation along a sensorimotor-association (S-A) axis. The paper is well-written, the logic is clear, and the figures effectively present the data.

I think that the identification of a transition period around age 15.5, where development shifts from sensorimotor strengthening to association network refinement, is a novel finding that advances our understanding of adolescent neurodevelopment. The authors also found that the S-A connectivity axis captures connectome-wide spatial variation in relationships between SC strength and both cognitive performance and psychopathology. These results support a hierarchical framework for SC development. The release of the interactive ConnectCharts is also a clear strength, as it will facilitate the reuse of these data.

Overall, I find the study rigorous and very likely to be of broad interest. Below, I have outlined several points and suggestions that would strengthen the current version of this manuscript:

1. The developmental turning point at ~ 15.5 yrs, in my view, is a major highlight of this study. However, given that this age range overlaps with puberty—a period known for sexual dimorphism in brain maturation. It is important to clarify if this timeline is consistent between both sexes. Did the authors test for Sex * Age interactions? Specifically, does the shift from sensorimotor to association refinement occur earlier in females? I am very

interested in a breakdown of the developmental trajectories by sex and think that would add significant biological nuance to the reported timeline.

1) 补充分析：在每条连接的发育模型中加 Sex*Age 交互项，检验交互是否显著。
2) 分开性别检验与 S-A axis 相关(Fig4b)的 shift age。

2. The authors define the S-A axis based on a priori biological properties. To better contextualize these findings within the broader field of network neuroscience, it would be valuable to see how this axis aligns with other established hierarchy maps. How strongly does your S-A connectional axis correlate with the principal gradient of functional connectivity (e.g., Margulies et al., 2016) or myelination maps (T1w/T2w ratios)? A comparison would help readers understand how your structural findings map onto the functional hierarchy of the cortex.

1) 增加 S-A axis 与 gradient 和 T1w / T2w 的相关。

3. The study argues for a specific gradient of change along the S-A axis. However, during development, there is often a global increase in white matter density. To confirm that the observed effects are regionally specific and not driven by whole-brain maturational trends, can the authors try regressing out the mean whole-brain structural connectivity strength? I am curious to see whether S-A gradient effects persist when controlling for global SC fluctuations.

1) 在做与 S-A axis 的相关时回归掉 whole-brain effects。

4. The manuscript links SC development to the "p-factor" of psychopathology. However, the discussion could be expanded to address the practical implications of this relationship. Please elaborate on the clinical applicability of these findings. How might clinicians eventually use these ConnectCharts to identify at-risk youth before severe symptoms emerge? A more detailed discussion of the potential clinical applications would make this section more informative for translational readers.

1) 增加讨论，典型发育轨迹的 clinical applications

5. How do the authors hypothesize that these white matter changes couple with gray matter morphology? Does the strengthening of sensorimotor connections precede the thinning of sensorimotor cortex?

1) 增加讨论

6. This study relies on a group-level parcellation. Given the recent focus on "precision functional mapping", we know that network boundaries can vary significantly across individuals, particularly in higher-order association zones. I suggest the authors discuss the use of group-level atlases versus individual-level parcellations as a limitation. It is worth acknowledging that while group-level analysis is necessary for these sample size,

future work using individual-level network mapping might reveal even stronger structure-function associations by accounting for topological variability at the individual level.

1) 在 limitation 里增加没有使用 individual atlas。

Minor points:

1. Page 4, lines 21-24: “We used 12 systems for the main analyses, representing an intermediate scale between the widely used 7- and 17-network frameworks, and confirmed robustness using both 7- and 17-system parcellations as well as the canonical Yeo-7 and Yeo-17 functional systems.” I think this phrasing is potentially confusing. I am not sure whether ‘7-network’ means that same standard ‘Yeo-7’ atlas or if the authors created their own subdivision of the S-A axis.

1) 修改表述

2. Fig. 1d. The current continuous color illustrates the S-A axis progression, but it makes it hard to see the exact spatial boundaries between adjacent systems on the cortical surface. It would be very helpful to provide a supplemental version using a discrete colomap (distnct, high-contrast color for each system). This would allow people to clearly see the specific cortical topography and boundary definitions of the 12 systems.

1) 在补充材料里放一个能清楚展示 S-A 12 systems 的图。

3. The capitalization of article titles is inconsistent. Please carefully standardlize the citation style throughout the reference section.

1) 文章中小标题格式统一，citation 格式检查。

Reviewer #1 (Remarks on code availability):

I have checked that overall the code is in a usable state and a motivated reader could reproduce the principal results of the paper

Reviewer #2 (Remarks to the Author):

This manuscript investigates the spatiotemporal development of structural connectivity across childhood and adolescence using large datasets. The authors propose that white

matter maturation follows a S-A connectional axis, with early strengthening of sensorimotor connections and late adolescence strengthening of association connections. They also identified a 'tipping point' around age 15.5 where the dominant developmental gradient shifts. The study benefits from rigorous replication across two independent datasets, but there are a few major concerns - several conceptual and methodological aspects need clarification, and further analyses are needed before the conclusions can be fully evaluated. Detailed comments follow.

Major issues:

1. The authors derive their S-A connectional axis directly from a pre-defined cortical S-A axis and then test whether developmental patterns align with this axis. This approach is inherently confirmatory rather than discovery-driven. Given that the S-A cortical axis was itself derived from multiple neurobiological properties including developmental gradients, finding that SC development aligns with this axis is perhaps unsurprising and potentially circular. Could the authors instead test out a data-driven analysis (e.g., PCA) on the developmental trajectories themselves to identify the dominant axis of variation, then compare the explanatory power of the S-A connectional axis against competing organizational principles? If not, this should be explained as to why not, and discussed as a limitation regarding interpretation of the findings.

批注 [A1]: 不确定这句话怎么理解。

1) 可以先对 S-A axis 进行解释，S-A axis 并没有包含 developmental gradients.
2) 对 developmental trajectories 进行 PCA，提取 PC1 loadings 做与 S-A connectional axis 的相关。

2. The correlation between SC-cognition effect sizes and S-A rank is rho = -0.22 with P = 0.056, which is not significant by conventional thresholds yet discussed as supporting the hypothesis. Effect sizes for individual connections should be reported. The authors should also discuss what magnitude of effect would be clinically meaningful, given that the current cognitive and psychopathological analyses reveal statistically significant but extremely small effect sizes in a massive sample (n > 7000 for ABCD).

1) 提供 SC-cognition 单条边的统计效应（r 值）
2) 讨论统计效应，可以用 neuron response 里之前回复的内容。

3. Methodological rigor of results- While the results are well written they are very general descriptions of findings and in many cases, not supported by any statistics in the text, e.g. ' Our analysis revealed variations in age effects across all 78 connections, with the strongest effects observed in connections among primary sensorimotor systems, moderate effects in connections among higher-order association systems, and the weakest effects in connections between sensorimotor and association systems.' Was there a statistical comparisons of effect size differences? Overall, more direct mapping of the statistical analysis to the specific results would be helpful.

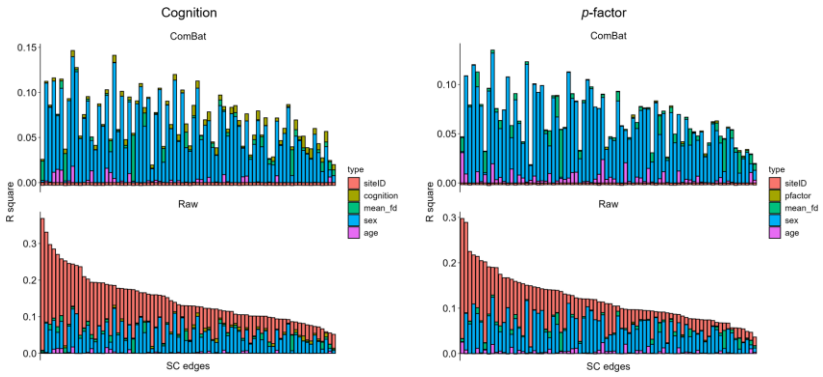
增加不同连接 effect size 的统计比较。

4. The authors mentioned that uncorrected standard scores of cognition (without age adjustment) were used for analysis. Could the authors provide more rationale for this approach?

1) 添加解释，但是似乎也没有特别强的理由。可以算个 corrected standard scores of cognition.

5. What are the considerations for including cognitive scores and p-factor into the covariates in the ComBat processing? I'm wondering how cognitive & clinical variances could impact the harmonization results. Could the authors examine the differences of including verse not including the cognitive and p-factor values and provide more detailed rationales?

1) 因为要保留 cognition & clinical 的效应。



6. Regarding the data harmonization with ComBat, I have a concern that this process may wash out microstructural effects in phenotypic variables that differed between sites. The authors might consider using Neuroharmonize (https://github.com/rpomponio/neuroHarmonize, Pomponio et al., 2020; NeuroImage), which is built off the ComBat algorithm but allows phenotypic differences to be preserved in the harmonization process, especially for developing age youth. Otherwise, is there a way the authors can show harmonization did not affect site differences that might be expected given phenotypic differences?

需要调研这个统计方法。

7. The p-factor approach, while increasingly popular, remains controversial. Using parent-reported symptoms in a population-based sample with restricted range may limit validity. Can the authors conduct sensitivity analyses with alternative psychopathology operationalizations that's available with ABCD or other datasets used in this study?

用 CBCL total raw 分做一下。

8. Despite having longitudinal data from ABCD and partial longitudinal data from devCCNP, the developmental trajectory analyses largely treat data as cross-sectional. The GAMMs with random intercepts account for repeated measures but do not leverage the longitudinal structure to test key claims about within-person developmental change. Statements like “developmental trajectories vary by cognition/psychopathology level” conflate between-person and within-person effects. Can the authors analyze the latent growth curve or multilevel models to explicitly test the within-person change?

需要先调研一下这些方法。

9. The “critical transition” at age 15.5 feels over-interpreted. The narrow CI of might suggest potential overfitting reflect the specific parameterization of GAM smoothing rather than a true biological discontinuity. The term “critical” implies a sensitive period with specific biological properties, which is not tested. I wonder if the longitudinal ABCD data show evidence of within-person transitions around this age.

ABCD 做不了这个工作，因为最大年龄也没到 15.5，可以思考一下。

Minor issues regarding language, typos and awkward wording:

1. P.10 Ln. 16: The alignment was “stale” before ~13 years -> should be “stable”

2. “pre-defined” “predefined” need to be standardized throughout

3. EFNY’s full name needs to be consistent throughout

4. hypothesized that the ‘spatiotemporal heterogeneity in SC development

would have implications in both cognitions’ – change to ‘hypothesized that the spatiotemporal heterogeneity in SC development would have implications *for both cognition*..’

5. Line 19 in Intro- cognition, not ‘cognitions’

6. Line 19/20 – “hypothesized that large-scale SC strength declined with better

cognitive performance..” ; change to ‘hypothesized that large-scale SC strength *would * decline with better cognitive performance

Reviewer #2 (Remarks on code availability):

I can confirm that detailed code is available but have not tried to implement it directly

Reviewer #3 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #3 (Remarks on code availability):

Reviewed the general integrity of codes but did not perform a detailed review of specific analysis scripts. Most analyses scripts are available on the github repository with a readme file.