Reviewed Preprint
v1 • March 10, 2026
Not revised

Reviewed Preprint
v2 • June 4, 2026
Revised by authors

Boosting Hyperalignment Performance with Age-specific Templates

Yuqi Zhang[1], **Maria Ida Gobbini**[2], **James V Haxby**[*,1], **Ma Feilong**[*,1,3] ✉

[1]Dartmouth College, Hanover, United States • [2]University of Bologna, Bologna, Italy • [3]University of South Carolina, Columbia, United States

✉ **For correspondence:**
feilong.ma@dartmouth.edu

[*] These authors contributed equally.

Competing interests: No competing interests declared

Funding: See page 11

Reviewing editor: Shuo Wang, Washington University in St. Louis, United States

eLife Assessment

This **valuable** study advances our understanding of best practices for analyzing population-level data using advanced functional alignment methods. It provides **convincing** evidence that demographic-specific functional templates improve functional neuroimaging studies that use hyperalignment. This study will be of interest to cognitive neuroscientists, neuroimaging methodologists, and computational researchers with an interest in the human brain.

https://doi.org/10.7554/eLife.110566.2.sa3

Abstract

Hyperalignment aligns individual brain activity and functional connectivity patterns to a common, high-dimensional model space, resolving idiosyncrasies in functional–anatomical correspondence and revealing shared information encoded in fine-grained spatial patterns. Given that the brain undergoes significant developmental and functional changes over the lifespan, it is likely that certain features in brain functional organization are more prominent in certain age groups than others. In this study, we examined whether age-specific functional templates, as compared to a canonical template, could enhance alignment accuracy across diverse age groups. We used the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset (18 to 87 yo) to build age-specific templates and tested their performance for analyzing data in young and old brains in both the Cam-CAN dataset and the Dallas Lifespan Brain Study (DLBS) dataset (20 to 90 yo). We found the congruent age-specific template outperforms the incongruent template for various analyses, including inter-subject correlation of hyperaligned connectivity profiles and predicting individualized connectomes and brain responses to the movie using the template. The results are consistent across both datasets. This work enhances our understanding of age-related differences in brain function, highlights the benefits of creating age-specific templates to refine hyperalignment model performance, and may contribute to the development of age-sensitive diagnostic tools and interventions for neurological disorders.

Introduction

Information encoded in the cortex can be decoded from fine-grained patterns of cortical activity via multivariate pattern analysis of fMRI data (Haxby et al., 2001, 2014). However, there is considerable variability across individual brains when encoding the same information (Cox & Savoy, 2003). Traditional approaches to brain alignment often fail to capture the fine-grained functional correspondence between brains due to topographic variability. Hyperalignment is a computational approach for modeling how the brain encodes shared information across individuals, despite individual variability in cortical topographies (Haxby et al., 2011, 2020). Hyperalignment can be trained using either brain responses (Haxby et al., 2011; Guntupalli et al., 2016) or functional connectivity (Guntupalli et al., 2018), and it captures both shared coarseand fine-scale information encoded in the brain. This approach also enhances the reliability of individual differences by affording analysis of differences in the fine-grained structure of the functional connectome (Feilong et al., 2018, 2021).

Given that the brain undergoes substantial developmental, structural, and functional changes across the lifespan, brain functional organization may demonstrate age-specific features that are not prominent in other age groups. These age-related variations can impact the alignment of neural data across individuals. Consequently, the performance of hyperalignment models in human connectomics may be significantly influenced by the age of the individuals used to build the templates. In this study, we investigate whether the incorporation of age-specific templates enhances the performance of hyperalignment models. Examining this aspect could not only improve hyperalignment accuracy across diverse age groups but also inform age-sensitive intervention strategies. Individual differences in the brain arise from both aging and neurological diseases and brain injuries. This knowledge also could open new pathways for creating more effective diagnostic tools for neurological disorders (Anderson et al., 2021, 2024).

We investigated this problem by developing age-specific hyperalignment templates using the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset and evaluating their performance with three indices: (a) inter-subject correlation (ISC) of connectomes, (b) prediction accuracy of individualized connectomes, and (c) prediction accuracy of individualized brain responses to the movie. Across all three analyses, we found consistent advantages of congruent age-specific templates (i.e., those constructed using data from the same age group) over incongruent templates. Together, these results demonstrate the importance of accounting for age-specific features of brain functional organization when applying functional alignment methods.

Methods

fMRI dataset

The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset comprises fMRI data of over 600 people from a cross-sectional adult lifespan (18 to 87 years old) population-based sample, with approximately 25 minutes of fMRI data per individual (Taylor et al., 2017). All MRI datasets were collected at MRC-CBSU using a 3T Siemens TIM Trio Scanner with a 32-channel head coil, 3.0 × 3.0 × 4.44 mm^3 voxels and 20% gap. Each individual’s fMRI data were collected during three different tasks:

1. 8 minutes 40 seconds of resting state with eyes closed (‘rest’);
2. 8 minutes of movie-watching of the film “Bang! You’re dead” (‘bang’);
3. 8 minutes 40 seconds of a sensorimotor task (‘smt’) during which participants were asked to press a button upon the presentation of a visual and/or auditory stimulus.

Both resting state and the sensorimotor task used single echo sequences with TR = 1970 ms, TE = 30 ms, flip angle = 78°, and the movie-watching task used multi-echo sequences with TR = 2470 ms, TEs = 9.4, 21.2, 33, 45, 57 ms, flip angle = 78°. 646 participants have the full records of all three functional scans (age distribution shown in Table 1).

Age Group	Age Range	Number of Participants	Training Group	Test Group
Young	18–45	215	144	71
Old	65–90	216	144	72

Table 1. **Age group division and corresponding training/test set sizes**

We classified the participants into three different age groups—young, mid, and old—with each group consisting of approximately the same number of individuals. Our analyses focus on the young and old groups.

Preprocessing

We preprocessed all MRI data using fMRIPrep (Esteban et al., 2019), with version 20.2.7. For each participant, the cortical surface was reconstructed using the high-resolution structural scans. The functional data were corrected for head motion, projected onto the cortical surface model, and resampled to the onavg-ico32 cortical surface template, which uniformly samples different parts of the cortex (Feilong et al., 2024). After that, we used linear regression to partial out nuisance regressors from our data. The list of nuisance regressors includes 6 head motion parameters and their derivatives, framewise displacement, global signal, 6 aCompCor components from cerebrospinal fluid and white matter, and polynomial trends up to the 2nd order. After the regression, we normalized the time series of each cortical vertex to zero mean and unit variance.

Individual connectome calculation

We computed two kinds of connectomes based on different functional scans:

1. using both resting state and sensorimotor task data,
2. using movie-watching data,

This division allows us to examine template performance using both functional connectivity and response time series to the movie. To calculate functional connectivity, we downsampled the data matrices for each individual and each task from ‘onavg-ico32’ space (19341 vertices) to ‘onavg-ico8’ space (1210 vertices) and used the time-series for downsampled data as connectivity targets. Correlations between connectivity target time-series and vertex time-series are indices of functional connectivity. Each vertex’s connectivity profile is a vector of 1210 elements, where each element is the correlation between the time series of the vertex and the time series of a connectivity target. We z-scored the connectivity profile for each of the 19341 vertices, and these connectivity profiles collectively form the connectome matrix of the individual and task.

Hyperalignment template creation

For each age group (young and old), we built the templates using approximately two thirds of the participants and withheld the remaining one third for testing. Given there are multiple ways to choose the participants, we repeated the procedure 10 times, each time randomly choosing two thirds of the participants without replacement. The participants used for evaluation were always independent from the participants used for training.

We combined fMRI data of different tasks to maximize the amount of data we use to compute the connectomes, given that differences in connectomes based on different tasks are much smaller in scale compared to individual differences (Gratton et al., 2018). Each whole brain template was created using a searchlight-based algorithm (Feilong et al., 2023, section 4.2) with a 20 mm searchlight radius, based on the training group participants’ connectome data calculated from the resting state data and sensorimotor task data. There are 19341 overlapping searchlights, each containing an average of approximately 121 vertices (range: 44 to 187). For each searchlight, we created a local template so that its representational geometry and topographies are representative of the training participants. We first concatenated the vertices of all participants and performed a PCA on the concatenated data, to derive a PC template that reflects the representational geometry of the searchlight, where $M_{(\mathrm{PC})}$ is the PC template,$B_{(p)}$ is the local data matrix of the p-th participant, and $n$is the number of participants.

$$M_{(PC)} = \frac{1}{\sqrt{n}}\mathrm{PCA}\left(B_{(1)}, \ldots, B_{(n)}\right)$$

We then applied a rotational matrix R to the PC template to minimize the topographic differences without changing the information content, where $\|\cdot\|_F$ is the Frobenius norm.

$$R = \arg\min_R \sum_{p=1}^{n} \left\| M_{(\mathrm{PC})}R - B_{(p)} \right\|_F^2$$

To find the solution R, we applied the orthogonal Procrustes algorithm to concatenated data matrices (see formula below).

$$R = \arg\min_R \left\| \begin{bmatrix} B_{(1)} \\ \vdots \\ B_{(n)} \end{bmatrix} - \begin{bmatrix} M_{(\mathrm{PC})} \\ \vdots \\ M_{(\mathrm{PC})} \end{bmatrix} R \right\|_F^2$$

The local templates $M_{(\mathrm{PC})}R$ searchlights were then combined to form the whole-brain template. For each participant p, we derived two transformation matrices using Procrustes algorithm: $R_{(p)}$, which projects data from the participant's native cortical space to the template space and was used in inter-subject correlation (ISC) analyses, and $R^{'}_{(p)}$, which projects data from the template space back to the participant's native cortical space and was used in the prediction analyses (Figure 1, see also Supplementary Figure 1). Note that these matrices differ from the rotation matrix R used to derive the local template.

Given that functional connectomes may differ across tasks, for each template based on resting state and sensorimotor data, we also computed a corresponding template based on the movie-viewing data. This was used in the analysis of predicting individual connectomes, as described below.

Inter-subject correlation (ISC)

We computed the inter-subject correlation (ISC) of connectivity profiles in the common model space to evaluate template performance, where higher ISCs indicate better performance. For each participant in the test set, we computed the participant's hyperalignment transformation matrix $R_{(p)}$ using the connectome based on resting state and sensorimotor task data, and applied the transformation matrix to the original movie-watching responses to compute the hyperaligned connectome. This ensures that the data used to compute hyperalignment transformation are independent from the data used to evaluate performance. We computed ISC as the correlation between the participant's connectivity profile and the average profile across other test participants in the same age group (Figure 1). Each participant has up to 20 ISC maps (10 young templates and 10 old templates), and we averaged ISC maps of the same kind (young or old) for each participant. We converted r values to z values (Fisher transform, arctanh(r)), averaged the z values, and converted them back to r values. Based on the analysis, we either averaged them across cortical vertices (Figures 2a, 2b, Supplementary 3a, 3b) or participants of the same age group (Figures 2c, Supplementary 3c).

Predicting individual connectome

We also tested the prediction of connectomes in held-out test participants' native anatomical space (Figure 1). We derived each participant's predicted movie-viewing connectome as the matrix multiplication of the movie-viewing template and the individual's transformation matrix $R^{'}_{(p)}$, derived from resting state and sensorimotor task data. We then compared the predicted connectome with the participant's actual movie-viewing connectome based on the correlation of the corresponding connectivity profiles in these two connectomes.

Predicting individual responses to the movie

Similarly, we predicted individual responses to the movie using the same templates created for the congruent and incongruent age groups. Using the Individualized Neural Tuning (INT) model (Feilong et al., 2023), each individual's connectome was modeled as the same template connectome with an individualized transformation, and we established correspondence between the modeled connectome and the brain responses to the movie using the same group of training participants used to build the template. In other words, we applied the INT model to enrich the template so that it could predict individualized brain responses in addition to individualized connectomes based on the template. We then evaluated the template's performance using correlation coefficients between the measured response time series to the movie and the predicted time series.

Figure 1. **Schematic of the procedure for building and testing hyperalignment templates.**

Darker arrows indicate congruent templates (i.e., from the same age group), whereas light arrows indicate incongruent templates.

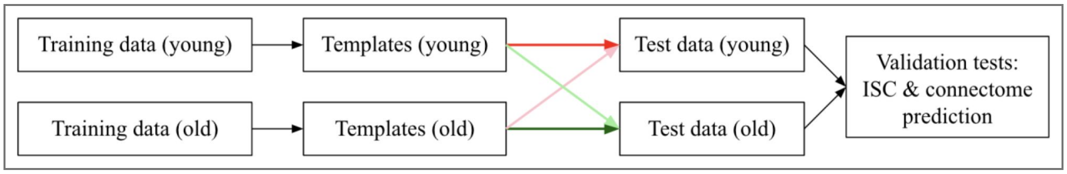
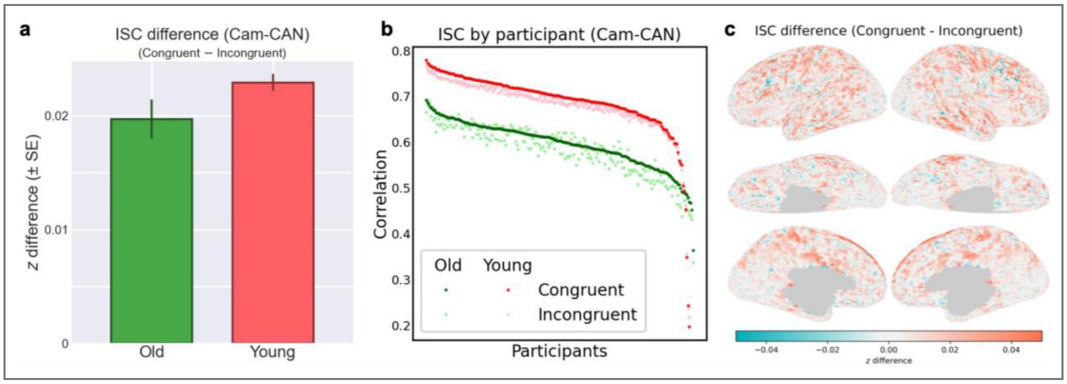


Figure 2. **Inter-subject Correlation Results (Cam-CAN).**

(a) The average z (± SD) for the old group was 0.6897 ± 0.0759 for congruent templates and 0.6700 ± 0.0839 for incongruent templates. The mean ISC difference (± SE) was 0.0197 ± 0.0017, $t(212) = 11.33$, Cohen's $d = 0.7766$ and $p < 10^{-22}$. The average z (± SD) for the young group was 0.8566 ± 0.1151 for congruent templates, and 0.8337 ± 0.1069 for incongruent templates. The mean ISC difference (± SE) was 0.0229 ± 0.0008, $t(209) = 30.09$, Cohen's $d = 2.0765$ and $p < 10^{-77}$. (b) Scatter plot of each participant's average ISC value derived from different congruent and incongruent templates. (c) Topographic distribution of ISC difference across different brain regions.



Validation dataset

The results based on the Cam-CAN dataset demonstrate that hyperalignment templates from the same age group work better than templates from age-incongruent templates, and this effect generalizes across tasks (from resting state and sensorimotor to movie-watching) and scan protocols (from single-echo sequences to multi-echo sequences). We further tested the generalizability of our results using an independent dataset—the DLBS dataset (Park et al., 2025), which was collected with a different scanner, a different group of participants, and different tasks (See Supplementary).

Results

We evaluated the performance of the templates using three metrics: (a) ISC of functional connectivity in the common template space, where higher ISCs indicate better alignment of connectivity in the template space; (b) similarity between model-predicted and measured connectomes in each participant's native anatomical space; and (c) similarity between model-predicted and measured neural responses to the movie, where higher similarity suggests the template contains more relevant information and better predicts individualized connectomes and movie responses. Across all metrics, we found that congruent age-specific templates outperformed age-incongruent templates.

Inter-subject correlation

We first evaluated the performance of templates constructed from both young and old age groups on ISCs of connectomes in the common model template space. We computed the z-difference (difference in Fisher z transformed correlations) between post-alignment ISC values derived from congruent and incongruent templates (Figure 2a). Hyperalignment based on congruent age-specific templates yields higher ISCs in both age groups, with a more pronounced effect in the young group. Breaking down the data by participant, we found that most participants (97.6% in the young group, 74.2% in the old group) exhibited higher ISCs when comparing the results for congruent and incongruent templates (Figure 2b). We also evaluated the ISC performance of an intermediate middle-aged cohort using a middle-aged template; these results are provided in Supplementary Figure 4. The topography of mean ISC differences displayed in Figure 2c illustrate that congruent templates perform better in the frontal, temporal, and parietal lobes. The ISC for the young group was consistently higher than that for the old group for both congruent and incongruent templates. This reflects, at least in part, differences in data quality between the two age groups (Supplementary Figure 2).

Predicting connectomes

Higher ISCs can arise from both (a) better alignment across participants and (b) filtering out noise during hyperalignment transformations. Though it is unlikely that our ISC results were driven by reduced noise, to rule out the possibility, we assessed how well different templates predict each participant's connectome.

For each individual, we calculated the correlation between the predicted connectome, generated using young and old training group hyperalignment templates calculated with rest and smt fMRI data, and the actual connectome, calculated using movie watching fMRI data. A higher correlation indicates a more accurate prediction, which means better performance of the hyperalignment template.

We compared the performance of congruent templates (built from the same age group) and incongruent templates (built from a different age group). For each participant in the test sets of both age groups, we calculated the predicted connectome using 20 templates—10 from each age group. We then computed the correlation for each participant and averaged the individual results across templates in the same age group. Figure 3a shows the z-difference between correlations calculated using congruent and incongruent templates for each participant in both groups. The results clearly indicate that predictions using congruent templates are more accurate than those using incongruent templates. Examining the participant breakdown in Figure 3b, we observed that almost all participants (98.6% in the young group and 94.4% in the old group) have a better connectome prediction using congruent templates than using incongruent templates from the other group. Additional results predicting the fine-grained connectome for the middle-aged cohort using the middle-aged template are detailed in Supplementary Figure 5. We also evaluated connectome prediction accuracies using templates constructed from 10-year age increments. The results show a continuous gradient of age-related divergence (Supplementary Figure 6). When predicting data for the 80–90 cohort, the 20–30 template performs the worst and the performance steadily improves as the template age gets closer to the target demographic. This systematic gradient further supports our main finding: the penalty for using an incongruent template increases with the discrepancy between the template age and participant age. The topographic distribution of mean differences between the predicted connectomes using congruent and incongruent templates are displayed in Figure 3c. Congruent templates generally perform better in the frontal and parietal lobes—regions primarily responsible for cognitive functions—which can be significantly influenced by age.

To evaluate the influence of age on the performance of hyperalignment template across the entire lifespan, we computed the correlation between actual connectome and predicted connectome of all participants using both young templates and old templates. As an individual's age becomes more distant from the template age group, the relative performance of the template decreases (Figure 4a, 4b).

Overall, congruent age-specific templates better predict participants' connectomes than incongruent templates. As the participant's age diverges further from the template age group, the prediction accuracy gets worse. This result indicates that age independent templates are necessary for improving the performance of hyperalignment.

Predicting brain responses to the movie

Besides functional connectivity, congruent templates also performed better than incongruent templates in predicting neural responses to the movie (Figure 5). These results indicate that the more congruent the template age group is with a participant's age, the more accurate the prediction becomes.

We used the same 10 functional templates for each age group, based on different participants randomly chosen as described earlier, to calculate individual transformation matrices and predict movie responses. We then focused on differences in performance between using congruent and incongruent templates.

Next, we computed correlation coefficients between the measured response time series to the movie and the predicted time series to evaluate template performance. The correlation coefficients were Fisher-transformed to *z* values and aggregated either across different parts of the brain (Figures 5a, 5b) or across participants (Figure 5c). Prediction performance for both groups was better when using congruent templates than incongruent templates, with the young group showing a larger congruency effect than the old group.

Discussion

In this paper, we analyzed the effect of age on hyperalignment performance. Our findings demonstrate the significant impact of age-specific hyperalignment templates on the accuracy of individualized connectome prediction, neural response to the movie, as well as the inter-subject correlation (ISC) values after hyperalignment.

The ISC results demonstrate the age effect on hyperalignment template performance. Average ISC values in the hyperalignment common model space are higher when projecting individual connectome to the common model space derived from congruent age group templates—those aligned with the participant's age group—rather than incongruent age group templates. By contrast, the congruency effect in the visual cortex is much smaller, suggesting that the aging effect on functional connectivity is smaller in these areas.

Figure 3. **Prediction performance comparison between congruent and incongruent templates.**

(a) The average *z* (± SD) for the old group was 0.4279 ± 0.0558 for congruent templates, and 0.4126 ± 0.0597 for incongruent templates. The mean difference of predicted connectome (± SE) was 0.0154 ± 0.0007, *t*(212) = 21.91, Cohen's *d* = 1.5014 and $p < 10^{-55}$. The average *z* (± SD) for the young group was 0.5716 ± 0.0779 for congruent templates, and 0.5568 ± 0.0743 for incongruent templates. The mean difference of predicted connectome (± SE) was 0.0147 ± 0.0004, *t*(209) = 39.07, Cohen's *d* = 2.6963 and $p < 10^{-97}$.(b) Scatter plot of each participant's average correlation value derived from different congruent and incongruent templates. (c) Topographic correlation difference across different brain regions.

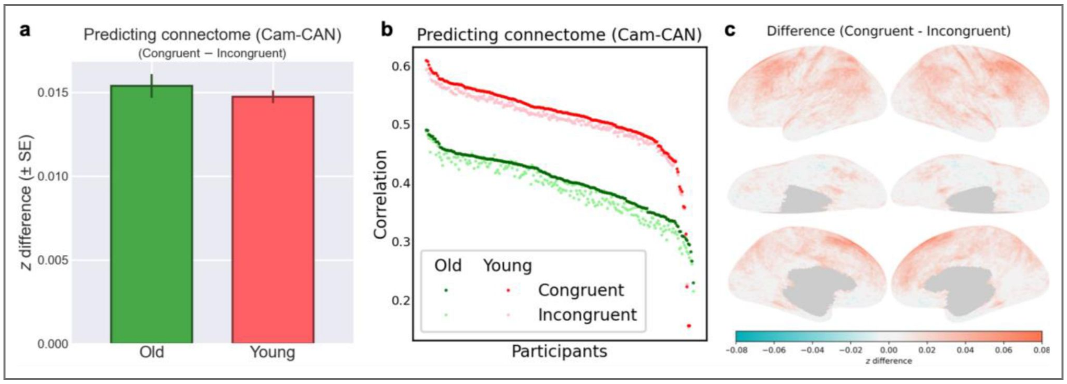
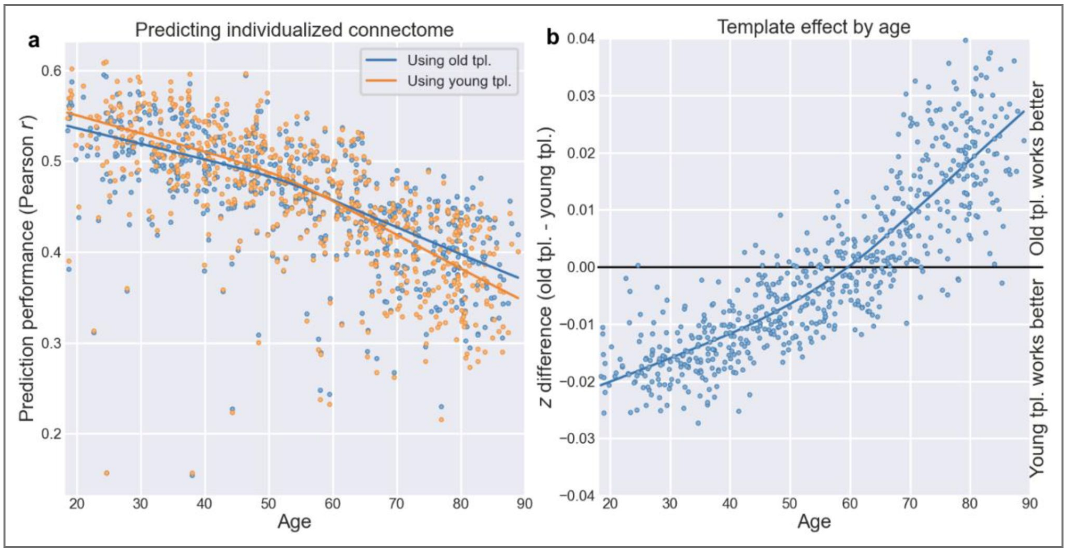


Figure 4. **Comparison of individual connectome prediction across all age spans.**

(a) Scatter plot showing Pearson correlation between actual connectome and predicted connectome derived from young and old templates for individuals across all age spans (b) Correlation difference among individuals between two age group templates, ordered by age.



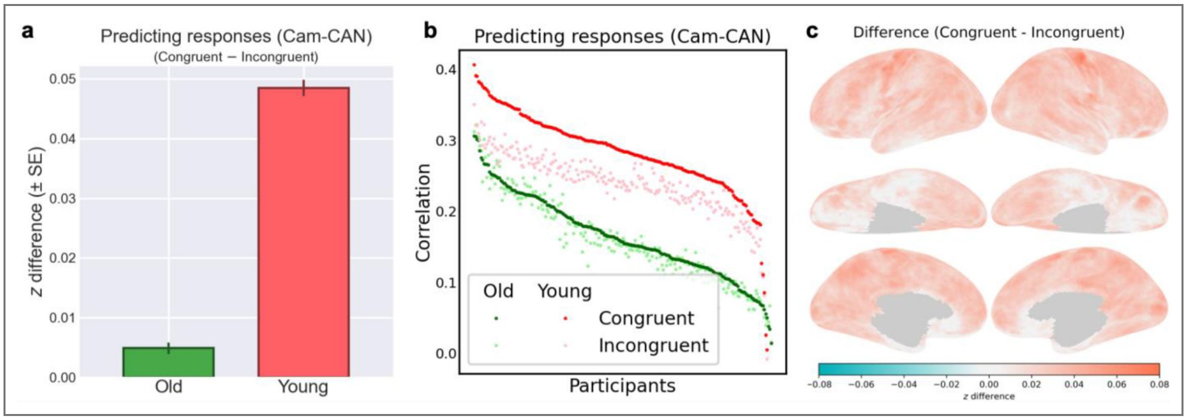


Figure 5. **Predicting brain responses to the movie based on congruent and incongruent templates.**

(a) The average z (± SD) for the old group was 0.1661 ± 0.0600 for congruent templates, and 0.1612 ± 0.0636 for incongruent templates. The mean difference (± SE) was 0.0049 ± 0.0010, $t(212) = 5.02$, Cohen's $d = 0.3443$ and $p < 10^{-5}$. The average z (± SD) for the young group was 0.2925 ± 0.0627 for congruent templates, and 0.2441 ± 0.0490 for incongruent templates. The mean difference (± SE) was 0.0485 ± 0.0013, $t(209) = 35.99$, Cohen's $d = 2.4833$ and $p < 10^{-90}$. (b) Scatter plot of each participant's average predicted response values derived from different congruent and incongruent templates. (c) Topographic distribution of predicted response difference across different brain regions.

Moreover, congruent hyperalignment templates consistently achieved higher correlation between predicted individual connectomes and actual connectomes in participants' native anatomical spaces compared to incongruent templates. When predicting an individual's connectome in different age groups using either old group templates (> 65 years old) or young group templates (< 45 years old), as the individual's age becomes more distant from the template age group, the prediction accuracy drops, and the difference between congruent and incongruent template prediction increases. Movie response prediction further indicates that the more congruent the template age group is with the participant's age, the more accurate the prediction becomes.

We applied ISC analysis to an independent dataset, DLBS, to further validate the generalizability of our findings (see Supplementary Material). The results were consistent with those observed in the Cam-CAN dataset, showing that congruent templates yielded higher average ISC values than incongruent templates.

Previous hyperalignment study shows that the more data used in building the templates for estimating individual tuning matrices, the better the model performs (Feilong et al., 2023). We expect, therefore, that the effect of age-congruency of templates will be greater if the templates are built with larger data sets. Currently, the templates are built using only approximately 16 minutes of fMRI functional data from around 200 participants. We expect that better and more stable model performance could be achieved by incorporating data from more participants and increasing the amount of data per participant, preferably to at least an hour. Moreover, incorporating data using richer stimulus paradigms in template construction might provide additional information that could enhance template performance. Currently our templates are constructed using only resting state and sensorimotor task data. Naturalistic stimuli, such as movie - viewing, more broadly sample cognitive and brain states. With increased data collection and richer, naturalistic stimulus paradigms, we could capture a broader range of neural activities and idiosyncrasies, potentially leading to more robust and flexible hyperalignment templates and a more precise and reliable alignment between individual connectomes and the common model space.

In this work, we only focused on the impact of age on hyperalignment templates and observed a significant improvement using congruent age templates compared to incongruent ones. Based on these findings, it is important to consider the practical applications of this methodology in future research. When the goal of a case-control study is to directly compare functional organization or brain responses between distinct populations—such as clinical and non-clinical participants—it is essential that all individuals are hyperaligned to the same common template. For these analyses, researchers should either construct a joint template containing a balanced, representative sample from both groups, or align all participants to a normative control template based on age-matched data. This ensures that the resulting data share a single coordinate system, allowing for valid statistical comparisons between groups.

Age-specific or disease-specific templates are highly advantageous when the research objective is to maximize decoding accuracy or predictive performance within a specific population. Just as age introduces specific variations in neural architecture, neurological or psychiatric conditions—such as Alzheimer's disease and Parkinson's disease—can produce alterations in brain structure and function. In clinical or lifespan research, if the goal is to build a reliable biomarker of differences among individuals within a group, e.g., of disease progression or disease subtypes, or to map individualized connectomes for a specific patient cohort, researchers should use a template congruent with that specific group. By constructing disease-specific templates, it may be possible to capture these distinctive neural patterns with greater accuracy, leading to more precise alignment of individual connectomes. This approach could provide insights into the pathophysiological mechanisms underlying various clinical conditions and broaden the use of hyperalignment models in clinical neuroscience.

Data availability

We have used two previous published dataset Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset (*https://opendata.mrc-cbu.cam.ac.uk/projects/camcan/*) and the Dallas Lifespan Brain Study (DLBS) dataset (*https://openneuro.org/datasets/ds004856*).

Additional files

Supplementary Materials.

Additional information

Funding

Funder	Grant reference number	Author
HHS | NIH | National Institute of Mental Health (NIMH)	5R01MH127199	James V Haxby

Author ORCID iDs

Yuqi Zhang: https://orcid.org/0009-0002-0687-1096
Maria Ida Gobbini: https://orcid.org/0000-0001-6727-7934
James V Haxby: https://orcid.org/0000-0002-6558-3118
Ma Feilong: https://orcid.org/0000-0002-6838-3971

References

Anderson Z., Gratton C., Nusslock R. (2021) The Value of Hyperalignment to Unpack Neural Heterogeneity in the Precision Psychiatry Movement. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* **6**:935-936 https://doi.org/10.1016/j.bpsc.2021.02.006 | PubMed

Anderson Z., Turner J. A., Ashar Y. K., Calhoun V. D., Mittal V. A. (2024) Application of hyperalignment to resting state data in individuals with psychosis reveals systematic changes in functional networks and identifies distinct clinical subgroups. *Aperture Neuro* **4** https://doi.org/10.52294/001c.91992 | PubMed

Cox D. D., Savoy R. L. (2003) Functional magnetic resonance imaging (fMRI) "brain reading":Detecting and classifying distributed patterns of fMRI activity in human visual cortex. *NeuroImage* **19**:261-270 https://doi.org/10.1016/s1053-8119(03)00049-1 | PubMed

Esteban O., Markiewicz C. J., Blair R. W., Moodie C. A., Isik A. I., Erramuzpe A., Kent J. D., Goncalves M., DuPre E., Snyder M., *et al.* (2019) fMRIPrep: A robust preprocessing pipeline for functional MRI. *Nature Methods* **16**:111-116 https://doi.org/10.1038/s41592-018-0235-4 | PubMed

Feilong M., Guntupalli J. S., Haxby J. V. (2021) The neural basis of intelligence in fine-grained cortical topographies. *eLife* **10**:e64058 https://doi.org/10.7554/eLife.64058 | PubMed

Feilong M., Jiahui G., Gobbini M. I., Haxby J. V. (2024) A cortical surface template for human neuroscience. *Nature Methods* **21**:1736-1742 https://doi.org/10.1038/s41592-024-02346-y | PubMed

Feilong M., Nastase S. A., Guntupalli J. S., Haxby J. V. (2018) Reliable individual differences in fine-grained cortical functional architecture. *NeuroImage* **183**:375-386 https://doi.org/10.1016/j.neuroimage.2018.08.029 | PubMed

Feilong M., Nastase S. A., Jiahui G., Halchenko Y. O., Gobbini M. I., Haxby J. V. (2023) The individualized neural tuning model: Precise and generalizable cartography of functional architecture in individual brains. *Imaging Neuroscience* **1**:1-34 https://doi.org/10.1162/imag_a_00032 | PubMed

Gratton C., Laumann T. O., Nielsen A. N., Greene D. J., Gordon E. M., Gilmore A. W., Nelson S. M., Coalson R. S., Snyder A. Z., Schlaggar B. L., *et al.* (2018) Functional Brain Networks Are Dominated by Stable Group and Individual Factors, Not Cognitive or Daily Variation. *Neuron* **98**:439-452.e5 https://doi.org/10.1016/j.neuron.2018.03.035 | PubMed

Guntupalli J. S., Feilong M., Haxby J. V. (2018) A computational model of shared fine-scale structure in the human connectome. *PLOS Computational Biology* **14**:e1006120 https://doi.org/10.1371/journal.pcbi.1006120 | PubMed

Guntupalli J. S., Hanke M., Halchenko Y. O., Connolly A. C., Ramadge P. J., Haxby J. V. (2016) A Model of Representational Spaces in Human Cortex. *Cerebral Cortex (New York, N.Y.: 1991)* **26**:2919-2934 https://doi.org/10.1093/cercor/bhw068 | PubMed

Haxby J. V., Connolly A. C., Guntupalli J. S. (2014) Decoding neural representational spaces using multivariate pattern analysis. *Annual Review of Neuroscience* **37**:435-456 https://doi.org/10.1146/annurev-neuro-062012-170325 | PubMed

Haxby J. V., Gobbini M. I., Furey M. L., Ishai A., Schouten J. L., Pietrini P. (2001) Distributed and Overlapping Representations of Faces and Objects in Ventral Temporal Cortex. *Science* **293**:2425-2430 https://doi.org/10.1126/science.1063736 | PubMed

Haxby J. V., Guntupalli J. S., Connolly A. C., Halchenko Y. O., Conroy B. R., Gobbini M. I., Hanke M., Ramadge P. J. (2011) A common, high-dimensional model of the representational space in human ventral temporal cortex. *Neuron* **72**:404-416 https://doi.org/10.1016/j.neuron.2011.08.026 | PubMed

Haxby J. V., Guntupalli J. S., Nastase S. A., Feilong M. (2020) Hyperalignment: Modeling shared information encoded in idiosyncratic cortical topographies. *eLife* **9**:e56601 https://doi.org/10.7554/eLife.56601 | PubMed

Park D. C., Hennessee J. P., Smith E. T., Chan M. Y., Chen X., Dakanali M., Farrell M. E., Liu P., Lu H., Rofsky N., *et al.* (2025) The Dallas Lifespan Brain Study: A Comprehensive Adult Lifespan Data Set of Brain and Cognitive Aging. *Scientific Data* **12**:846 https://doi.org/10.1038/s41597-025-04847-7 | PubMed

Taylor J. R., Williams N., Cusack R., Auer T., Shafto M. A., Dixon M., Tyler L. K., Henson R. N. (2017) The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) data repository: Structural and functional MRI, MEG, and cognitive data from a cross-sectional adult lifespan sample. *NeuroImage* **144**:262-269 https://doi.org/10.1016/j.neuroimage.2015.09.018 | PubMed

Taylor JR, Williams N, Cusack R, Auer T, Shafto MA, Dixon M, Tyler LK, Cam-CAN, Henson RN (2017) Structural and functional MRI, MEG, and cognitive data from a cross-sectional adult lifespan sample. Cambridge Centre for Ageing and Neuroscience (Cam-CAN) data repository. https://opendata.mrc-cbu.cam.ac.uk/projects/camcan/

Park DC, Hennessee JP, Smith ET, Chan MY, Chen X, Dakanali M, Farrell ME, Liu P, Lu H, Rofsky N, *et al.* (2025) The Dallas Lifespan Brain Study: A Comprehensive Adult Lifespan Data Set of Brain and Cognitive Aging. OpenNeuro. ID ds004856 https://openneuro.org/datasets/ds004856

Peer reviews

Reviewer #1 (Public review):

The authors present a compelling case for the necessity of age-specific templates in functional hyperalignment. Given that the brain undergoes substantial developmental, structural, and functional changes across the lifespan, a 'one-size-fits-all' canonical template is often insufficient. This study effectively demonstrates that incorporating age-congruent features significantly enhances the performance and sensitivity of hyperalignment models. By validating these findings across two independent datasets (Cam-CAN and DLBS), the paper provides robust evidence that accounting for age-related functional organization is a critical prerequisite for accurate functional alignment in lifespan research

Comments on revised version:

The authors have been exceptionally thorough in addressing the concerns raised by the reviewers. In particular, the inclusion of the supplemental analysis on the middle-aged cohort is a valuable addition that strengthens the manuscript. Furthermore, the rationale for employing a congruent template is well-articulated; this approach clearly provides a more robust and accurate foundation for reconstructing individualized connectomes. I appreciate the authors' detailed responses and have no further comments.

https://doi.org/10.7554/eLife.110566.2.sa2

Reviewer #2 (Public review):

Summary:

In this study, Zhang and colleagues examine the role of participant selection in creating and using functional templates to improve analyses using hyperalignment. Hyperalignment aligns participants' functional MRI data to a shared functional template, analogous to the anatomical templates used to bring anatomical MRI data into a shared space (e.g., MNI152). The question of appropriate template creation is especially pressing for population-level analyses, where a large number of demographic groups (e.g., different age ranges, clinical statuses) may be included in the same analysis. These different demographic groups may have differences in their functional organization that complicate the creation of a single study-specific functional template.

To provide an initial investigation of the potential effect of demographic-specific templates, the authors use the publicly available Cam-CAN dataset which contains participants from 18 to 87 years of age. They define a young adult (< 45 years of age) and an older adult group (> 65 years of age) from this dataset with approximately the same number of participants. They investigate whether "age-congruent" templates (i.e. defined in the same age group they are used) improve three analyses where hyperalignment has been previously shown to boost performance: inter-subject correlation, predicting individual connectomes, and predicting individual functional responses. Using the Cam-CAN derived older adult template, they then replicate the ISC analyses using the publicly available Dallas Lifespan Brain Study (DLBS).

Overall, the presented results are highly suggestive that age-congruent templates consistently improve performance, though the absolute effects are small.

Strengths:

The use of a separate validation sample-re-using the same template calculated with Cam-CAN-highlights the potential of developing independent templates for individual demographic groups and then distributing these for wider use, analogous to the MNI templates that are widely used throughout the field of neuroimaging. This suggests that the potential impact of this framework is significant.

Weaknesses:

In their revision, the authors have addressed the previously raised "weaknesses" by providing guidance for researchers interested in using age-specific hyperalignment templates in practice.

Impact:

Overall, this work is likely to encourage future development of age-specific functional templates in the imaging community.

https://doi.org/10.7554/eLife.110566.2.sa1

Author response:

The following is the authors’ response to the original reviews.

> ***Public Reviews:***
>
> ***Reviewer #1 (Public review):***
>
> *Summary:*
>
> *The authors present a compelling case for the necessity of age-specific templates in functional hyperalignment. Given that the brain undergoes substantial developmental, structural, and functional changes across the lifespan, a 'one-size-fits-all' canonical template is often insufficient. This study effectively demonstrates that incorporating age-congruent features significantly enhances the performance and sensitivity of hyperalignment models. By validating these findings across two independent datasets (Cam-CAN and DLBS), the paper provides robust evidence that accounting for age-related functional organization is a critical prerequisite for accurate functional alignment in lifespan research.*
>
> *Strengths:*
>
> *(1) The authors used three metrics to evaluate performance. Across all metrics, they found that age-congruent templates outperformed age-incongruent templates, suggesting that age-specific templates can improve alignment.*
>
> *(2) These findings highlight the superiority of age-congruent templates for hyperalignment. This work underscores the importance of age-matching in cross-subject functional mapping and represents a vital step forward for the methodology.*

We thank the reviewer for the summary and the positive evaluation of our manuscript.

> *Weaknesses:*
>
> *(1) Participant Demographics and Group Separation:*
>
> *The study defines the 'older' cohort as 65-90 years and the 'younger' cohort as 18-45 years. While this 20-year gap (ages 46-64) effectively maximizes the contrast between groups, the results in Figure 4a suggest that the predicted individualized connectomes follow a continuous distribution. Given this continuity, could the authors provide the average median trends for Figures 2a and 2b to illustrate how the model behaves across the missing age range?*

Thanks for raising this important point. We had calculated the results for the middle-aged cohort template and have included them in the Supplementary Figures 4 & 5. Similar to Figure 2a, 2b, 3a and 3b, we directly compare the intersubject correlation and prediction performance of the middle-aged participants when aligned to their congruent middle-aged template versus an incongruent template. We observed consistent results across validation analyses (ISC and prediction) and groups (young vs. middle-aged, middle-age vs. old). Consistent with our main findings, the middle-aged cohort exhibits significantly higher intersubject correlation and prediction performance when using the age-congruent middle-age template. These results confirm that the age-related shifts in functional brain organization captured by the hyperalignment templates follow a continuous trajectory across the lifespan.

> *(2) Request for Implementation:*
>
> *I have been unable to locate the source code associated with this publication. Could the authors please provide a link to the repository or clarify if the implementation is available for reproduction?*

We have made our scripts public in GitHub and here’s the link: *https://github.com/yuqi98/Aging_templates_scripts*

> *(3) Analysis of Prediction Performance and Distribution:*
>
> *While Figures 3b and 5b clearly demonstrate that the congruent template improves correlation, Figure 4a shows a distinct shift in the scatter distribution. Could the authors provide a detailed explanation of the prediction performance metrics used? Specifically, I would like to understand how the underlying method accounts for the distribution differences observed when applying the congruent template.*

Our prediction performance metric is the average Pearson correlation. We calculated the correlation between the model-predicted data (the individualized connectome in Figure 3 and the movie response in Figure 5) and the participant's actual measured data for each cortical vertex and averaged the correlations across vertices. A higher correlation indicates that the group template, when combined with the participant’s individualized transformation matrix, more accurately reconstructs the individualized functional connectome and responses to stimuli.

The distinct upward shift in prediction performance when using a congruent template occurs because brain functional organization shows age-specific features. A congruent template captures these age-specific connectivity and response features. Importantly, the template creation algorithm aims to reflect the central tendency of the training data, including representational/connectivity geometry and functional topographies. Therefore, the observed differences in templates reflect differences in functional organization across age groups. As a result, when projecting the common template back into an individual’s native cortical space using the transformation matrix derived from independent data, the congruent template provides a richer, more accurate basis for reconstructing the individualized connectome and movie-watching responses.

> ***Reviewer #2 (Public review):***
>
> *Summary:*
>
> *In this study, Zhang and colleagues examine the role of participant selection in creating and using functional templates to improve analyses using hyperalignment. Hyperalignment aligns participants' functional MRI data to a shared functional template, analogous to the anatomical templates used to bring anatomical MRI data into a shared space (e.g., MNI152). The question of appropriate template creation is especially pressing for population-level analyses, where a large number of demographic groups (e.g., different age ranges, clinical statuses) may be included in the same analysis. These different demographic groups may have differences in their functional organization that complicate the creation of a single study-specific functional template.*
>
> *To provide an initial investigation of the potential effect of demographic-specific templates, the authors use the publicly available Cam-CAN dataset, which contains participants from 18 to 87 years of age. They define a young adult (< 45 years of age) and an older adult group (> 65 years of age) from this dataset with approximately the same number of participants. They investigate whether "age-congruent" templates (i.e. defined in the same age group they are used) improve three analyses where hyperalignment has been previously shown to boost performance: inter-subject correlation, predicting individual connectomes, and predicting individual functional responses. Using the Cam-CAN-derived older adult template, they then replicate the ISC analyses using the publicly available Dallas Lifespan Brain Study (DLBS).*

> *Overall, the presented results are highly suggestive that age-congruent templates consistently improve performance, though the absolute effects are small.*
>
> *Strengths:*
>
> *The use of a separate validation sample, reusing the same template calculated with Cam-CAN, highlights the potential of developing independent templates for individual demographic groups and then distributing these for wider use, analogous to the MNI templates that are widely used throughout the field of neuroimaging. This suggests that the potential impact of this framework is significant.*

We thank the reviewer for the summary and the positive evaluation of our manuscript.

> *Weaknesses:*
>
> *While the authors appropriately highlight the potential applications of this result (e.g., to different clinical statuses), it is not apparent how to appropriately extend this methodology to many common experimental paradigms. For example, in case-control studies (where researchers are interested in comparing clinical and non-clinical participants) the use of two different functional templates may complicate rather than ease analyses. Providing this as a potential limitation of the current template construction method, or providing recommendations to researchers interested in comparing across groups, would help to increase the impact of this work.*

We appreciate the reviewer raising this important practical consideration. We have added additional explanation to the Discussion section to provide clear recommendations for researchers applying this methodology, which we summarize below:

When the goal of a case-control study is to directly compare functional organization or brain responses between clinical and non-clinical participants, it is essential that all individuals are hyperaligned to the same common template. For these analyses, researchers should either construct a joint template containing a balanced, representative sample from both groups, or align all participants to a normative control template. This ensures that the resulting data share a single coordinate system, allowing for valid statistical comparisons between groups.

However, disease-specific or age-specific templates are highly advantageous when the research objective is to maximize decoding accuracy or predictive performance within a specific population. In real world clinical or lifespan research, if the goal is to build a reliable diagnostic biomarker for disease progression or map individualized connectomes for a specific patient's cohort, researchers should use a template congruent with that specific group. The congruent template will preserve the group-specific representational geometry, providing a better individual-level prediction than a general cortical template.

> ***Recommendations for the authors:***
>
> ***Reviewer #2 (Recommendations for the authors):***
>
> *In general, there appears to be significantly more spread in the values for older adults (e.g., Figure 4b). It would be useful to know whether subdividing this group improves its relative performance; however, this will likely require additional investigation into the number of participants needed to establish a minimal template.*

We thank the reviewer for this constructive comment. We agree that older adults exhibit greater inter-individual variability in functional organization, which likely drives the larger spread observed in Figure 4b. We also appreciate the suggestion to subdivide this group to see if narrower age bins improve relative performance.

We have constructed templates using narrower, 10-year age intervals and evaluated their performance. Because model performance increases with the amount of training data, we use a fixed number of training participants for each age group (two thirds of the people from the group with the minimal number of people) to build the templates to make a fair comparison. We have added the results in the Supplementary Figure 6. The results show a continuous gradient of age-related divergence. When predicting data for the 80–90 cohort, the 20–30 template performs the worst and the performance steadily improves as the template age gets closer to the target demographic. This systematic gradient further supports our main finding: the penalty for using an incongruent template increases with the discrepancy between the template age and participant age.

Interestingly, we noticed that at the extreme ends of the age range (20–30 and 80–90), the strictly congruent template was slightly outperformed by the immediately adjacent age bin (i.e., the 30–40 template for young participants, and the 70–80 template for the oldest participants). Because we strictly matched the number of training subjects across all bins, this slight dip is likely driven by differences in raw data quality. It is common for fMRI data from the extreme ends of the lifespan to have slightly lower signal-to-noise ratios or higher head motion compared to the intermediate 30–40 or 70–80 cohorts. This suggests that while age congruency is a key driver of hyperalignment success, the intrinsic data quality of the cohort used to build the template also plays a practical role in its overall performance.

This brings up the reviewer's second point regarding the number of participants needed to establish a minimal template. Subdividing the age groups reduces the sample size available to construct each template. Previous research has demonstrated that while a hyperalignment template derived from a relatively small number of participants can achieve acceptable performance, increasing the amount of data and the number of subjects in the template space consistently and robustly improves alignment quality (See Supplementary Figure 7 in Feilong et al., 2023). Ultimately, our long-term goal is to build highly robust, standardized templates for fine-grained age cohorts across the entire lifespan. We are preparing to collect large-scale datasets from age 20 to 100 to build age-specific templates and provide them as open resources. This will allow future researchers to directly align their data to an age-appropriate template without needing to construct one from their own limited samples.

Reference

Feilong, M., Nastase, S. A., Jiahui, G., Halchenko, Y. O., Gobbini, M. I., & Haxby, J. V. (2023). The individualized neural tuning model: Precise and generalizable cartography of functional architecture in individual brains. Imaging Neuroscience, 1, 1–34. *https://doi.org/10.1162/imag_a_00032*

https://doi.org/10.7554/eLife.110566.2.sa0