# Responses to reviewer comments

We thank the reviewers for their careful reading of the manuscript and a number of valuable suggestions. To address these comments, we performed additional analysis and made several changes to the manuscript as summarized below:

## Reviewer #1.

*Comment 8: The authors claim that the sparse + latent model still outperforms the other models when they the convex approach to estimate the precision matrix. However, the number of latent factors they find when they use this convex approach is now 72, significantly higher than the number found in the first version of the paper where fixed number of latent dimensions was assumed. The number in that case was ~15. Why is that the case? Is it because a lot of the latent factors explain very little variance? In that case, how much does the performance drop if they are removed (e.g. through thresholding)? Could this difference also have to do with the fact that a different cross-validation function was used? I think this should be clarified since a number of 72 factors out of a total of ~300 cells does not necessarily imply a "very low rank" structure.*

There was considerable variability across sites with respect to the number of latent variables and the sparsity of the sparse component (Fig. 5 B and C in main text). The increase in the number of latent variables and the increase in the sparsity of the sparse component between the first and the second revision was the sum effect of three changes:

1. **Corrected the estimation of the mean response during cross-validation.**  In the original submission, the mean response was subtracted before cross-validation. We later realized that estimating the mean responses outside the cross-validation loop introduced a bias to the optimal hyperparameter values. In resubmitted manuscript, all parameters (mean, variance, correlations) were independently estimated in each cross-validation fold.
2. **Corrected the estimation of the variances.**  In the first submission, the variances of the activity of individual neurons were not conditioned on the stimulus. Effectively, a single covariance matrix was estimated across all conditions, which was only subsequently used to compute the correlation matrix. This was not different from similar covariance estimation in other applications (e.g. fMRI or gene interaction networks). However, we realized that the assumption of uniform vaiances introduced a bias exaggerating the effect of tuning similarity on correlations. In the second submission, we conditioned the variances on the stimulus and only assumed a constant correlation matrix across all conditions. This procedure was described in the Methods section. Conditioning the variances contributed to shifting the balance from pairwise interactions to latent variables.
3. **Replaced fixed latent factors (generally non-convex optimization problem) with nuclear norm penalty (convex optimization).** In the second submission, the sparse+latent regularization scheme was from a fixed number of latent units to nuclear-norm penality. This formulation of the problem penalizes for both the number of latent units and the magnitude of their interactoins, favoring a greater number of latent units.

The figure below compares Fig 5 B and C in the original submission (top row) and the revised submission (bottom row). The middle row shows the result after making the first two changes but not the third. The increase in latent variables is mostly due the conditioning of variances on the stimulus and estimation of the means separately within each fold of cross-validation.



*Comment 8: I think some discussion on what the nuclear norm is, and why it coincides with the trace should be added in the main text.*

In the revised manuscript, added an explanation of the nuclear norm penalty in the Methods section, accompanying Eq. 17, with additional references.

*Reviewer #2: The authors have substantially improved the manuscript. One important comment, however, has not received in my opinion adequate attention. In my previous review, I proposed comparing the regularized estimates of covariances to the true one by using a generative model that is not Gaussian. A straightforward exercise to address the robustness of the proposed regularization methods against more realistic scenarios (non-negative signal values arising from spike counts, a process that cannot be strictly Gaussian) would be generating a covariance matrix where spike trains of N neurons consist of the sum of a Poisson process independent across cells, plus a common Poisson process that is shared to all cells (there is no need of generating a spiking network to draw samples from this simple generative model). This would correspond to a single non-Gaussian latent cause plus independent noise. What regularization methods describe better the underlying process? Although I am proposing this example, any other similar simple example with non-Gaussian processes would be sufficient.*

To address this comment, we reproduced the simulation results in Fig. 1 using the pairwise Ising models instead of Gaussian. A detailed explanation accompanies Eq. 11 in the new revision of the manuscript. Figure S1 shows the evaluation results, which closely matched the results from the Gaussian models.

We have further removed the supplementary figure and accompanying discussion of using other loss functions (e.g. quadratic loss function), which was used to demonstrate that the assumption of Gaussianity was not strict. We think that the newly added simulation result more clearly demonstrates lack of strong dependence on the Gaussianity of the data-generating process.

# Additional improvements

We have also simplified Figure 6 by replacing averaged normalized plots of correlations and connectivities with non-normalized results for each of the five plots. This allowed simplifying the explanation in the caption.