Parcellation of brain lesions using a precomputed human brain connectome improves lesion symptom localization

William Drew[1], Alexander L. Cohen[1,2,3,4], Amy Brodtmann[5], Maurizio Corbetta[6,7], Natalia Egorova-Brumley[8,9], Sophia Gozzi[10,11], Jordan Grafman[12,13], Andrew M. Naidech[12], Joel L. Voss[12], Thomas Yeo[14,15,16,17,18,19], Michael D. Fox[1,2,20], Shan H. Siddiqi[1,2,21]

[1]Center for Brain Circuit Therapeutics, Brigham and Women's Hospital, [2]Harvard Medical School, Harvard University [3]Department of Neurology, Boston Children's Hospital, [4]Computational Radiology Laboratory, Boston Children's Hospital [5]Melbourne Neuropsychiatry Centre, The University of Melbourne, [6]Department of Neuroscience, Padova Neuroscience Center (PNC), Venetian Institute of Molecular Medicine (VIMM), University of Padova [7]Departments of Neurology, Radiology, Bioengineering, and Neuroscience, Washington University, [8]Melbourne School of Psychological Sciences, University of Melbourne, [9]The Florey Institute of Neuroscience and Mental Health, [10]Department of Neurology, Monash Health, [11]Department of Medicine, School of Clinical Sciences, Monash University[12]Feinberg School of Medicine, Northwestern University, [13]Shirley Ryan AbilityLab, [14]Martinos Center for Biomedical Imaging, Massachusetts General Hospital [15]Centre for Sleep & Cognition, Yong Loo Lin School of Medicine, National University of Singapore [16]Centre for Translational Magnetic Resonance Research, Yong Loo Lin School of Medicine, National University of Singapore, [17]Department of Electrical and Computer Engineering, National University of Singapore [18]Institute for Health, National University of Singapore [19]Institute for Digital Medicine, National University of Singapore [20]Department of Neurology, Harvard Medical School [21]Department of Psychiatry, Harvard Medical School

Introduction

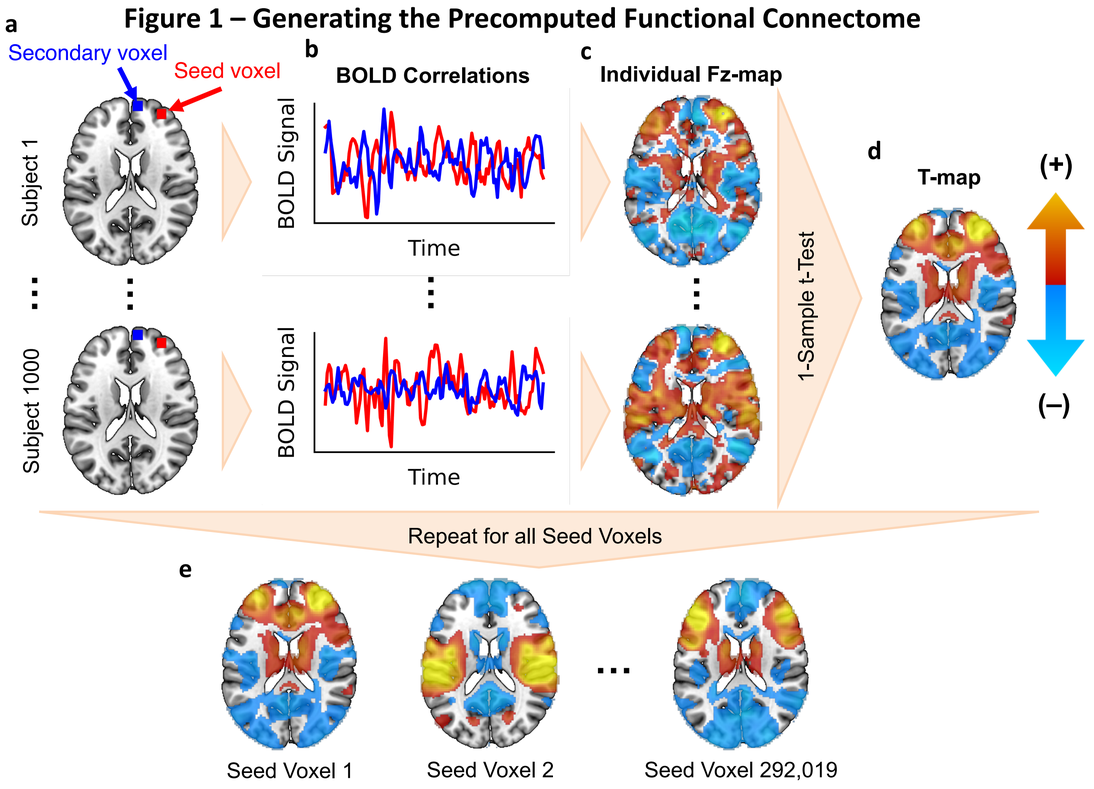
Lesion network mapping (LNM) uses brain lesions to link symptoms to functional brain networks causally. **However, LNM has two main limitations** when computing lesion functional connectivity maps.

1. LNM is **computationally inefficient**, inhibiting the effective use of large connectome datasets like the 40,000+ subject UK Biobank.
2. LNM **assumes a brain lesion is homogeneously connected to a single functional brain network**. However, lesions may span multiple functionally distinct brain regions and networks, potentially introducing noise.

Methods

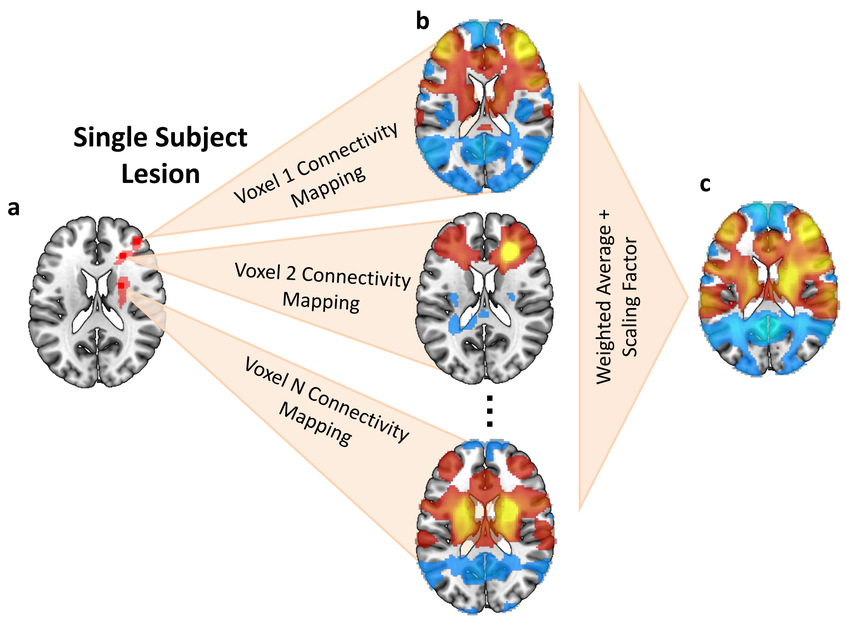
- **We created a precomputed human brain connectome (PHBC)** using mean whole-brain functional connectivity of 292,019 8mm^3 brain voxels across 1,000 healthy participants. The precomputed functional connectome is a high-resolution atlas of voxel-wise functional connectivity.
- **We developed the precomputed LNM method to compute lesion functional connectivity maps efficiently.** The precomputed method uses the PHBC to calculate a weighted average of the functional connectivity maps corresponding to voxels in an ROI. Next, a scaling factor is applied to account for differences between individual voxel BOLD signal strengths.
- **We developed a method to parcellate brain lesions to reduce the effect of heterogenous brain networks.** For each lesion, a connectivity matrix of voxel-pairwise connectivity is extracted, thresholded to remove weak connections, and then clustered using **Infomap** to group voxels into clusters with similar connectivity profiles.

Figure 1 – Generating the Precomputed Functional Connectome



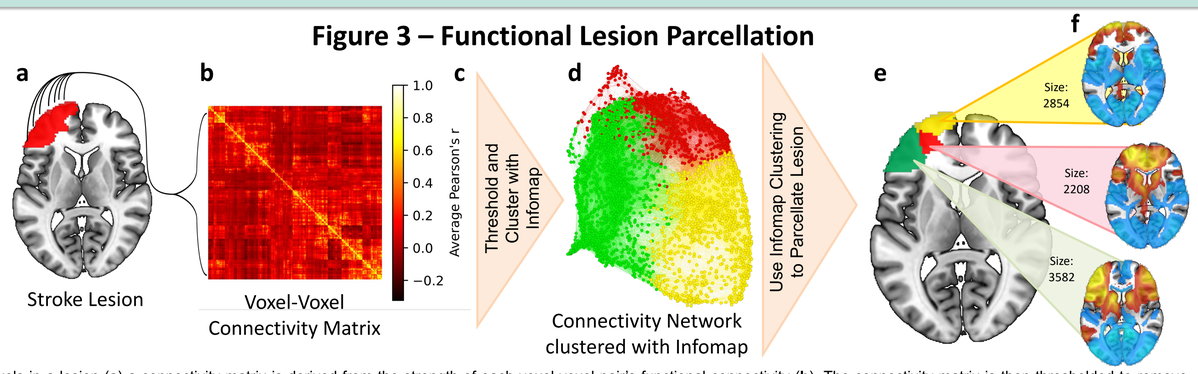
(**a**) For a seed voxel, another voxel in the brain is selected across all subjects in the resting state functional connectivity MRI connectome. (**b**) The blood oxygen level dependent (BOLD) timecourse signal in those subjects at rest at the selected voxels is extracted, Pearson correlated together, and Fisher z-transformed. This is repeated for every pair of voxels between the brain and the seed voxel to compile the individual Fz-map (**c**). The individual Fz-map contains the functional connectivity from every voxel in the brain to the seed voxel in the individual subject in the connectome. Next, a voxel-wise one-sample t-test is computed across the individual Fz-maps to compile the T-map (**d**). Steps (**a-d**) are repeated for every seed voxel in the brain and compiled to form the precomputed functional connectome (**e**).

Figure 2 – Precomputed Lesion Network Mapping



For each individual source voxel in the seed ROI (**a**), corresponding functional connectivity T-maps are retrieved from the precomputed functional connectome (**b**). The T-maps are weighted by the standard deviation of the source voxel BOLD signal, and then averaged together to generate a T-map corresponding to the functional connectivity relative to the whole seed ROI. A scaling factor calculated from the standard deviations of the source voxel BOLD signals is applied.(**c**).

Figure 3 – Functional Lesion Parcellation

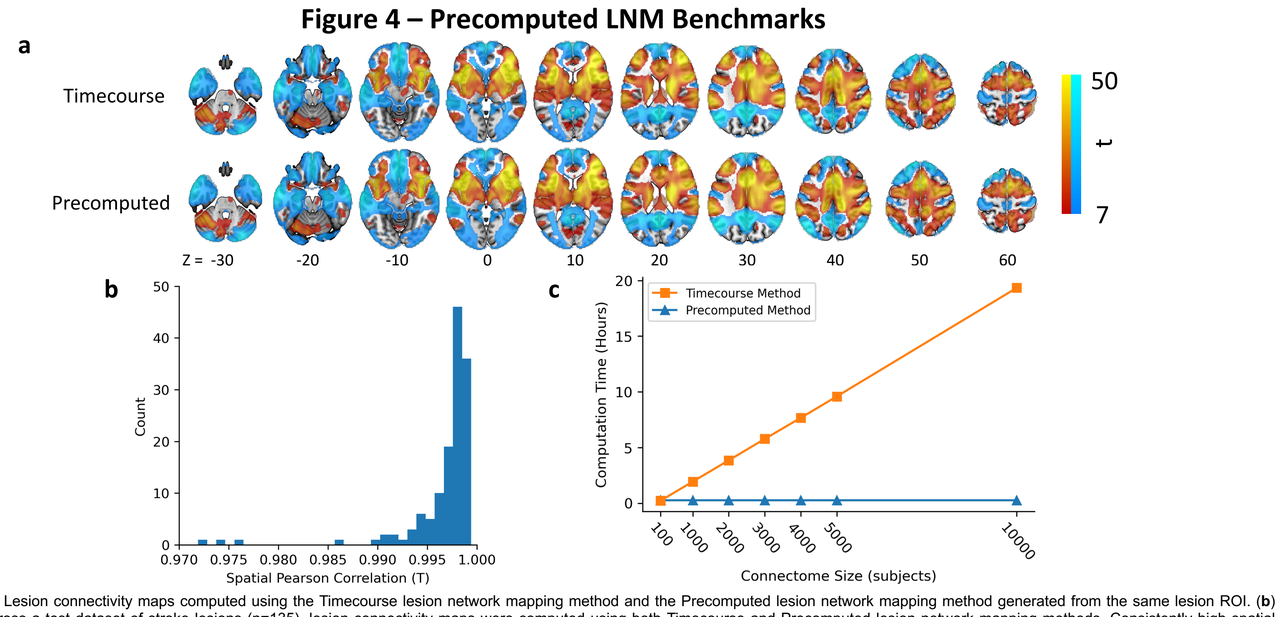


For each pair of voxels in a lesion (**a**) a connectivity matrix is derived from the strength of each voxel-voxel pair's functional connectivity (**b**). The connectivity matrix is then thresholded to remove weak connections between pairs of voxels and interpreted as a network where each voxel is a node and the strength of the functional connectivity between each pair of voxels is simulated by the strength of a spring connecting the two respective nodes of the network (**c**). Infomap is used to parcellate the network into neighborhoods of voxels with high in-group connectivity (**d**). These neighborhoods of voxels are then converted back into individual parcels indicating functionally homogenous parcels that make up the original lesion (**e**). Functional connectivity maps are generated for each parcel, but only the largest parcel by volume is selected for further analysis (**f**).

Results

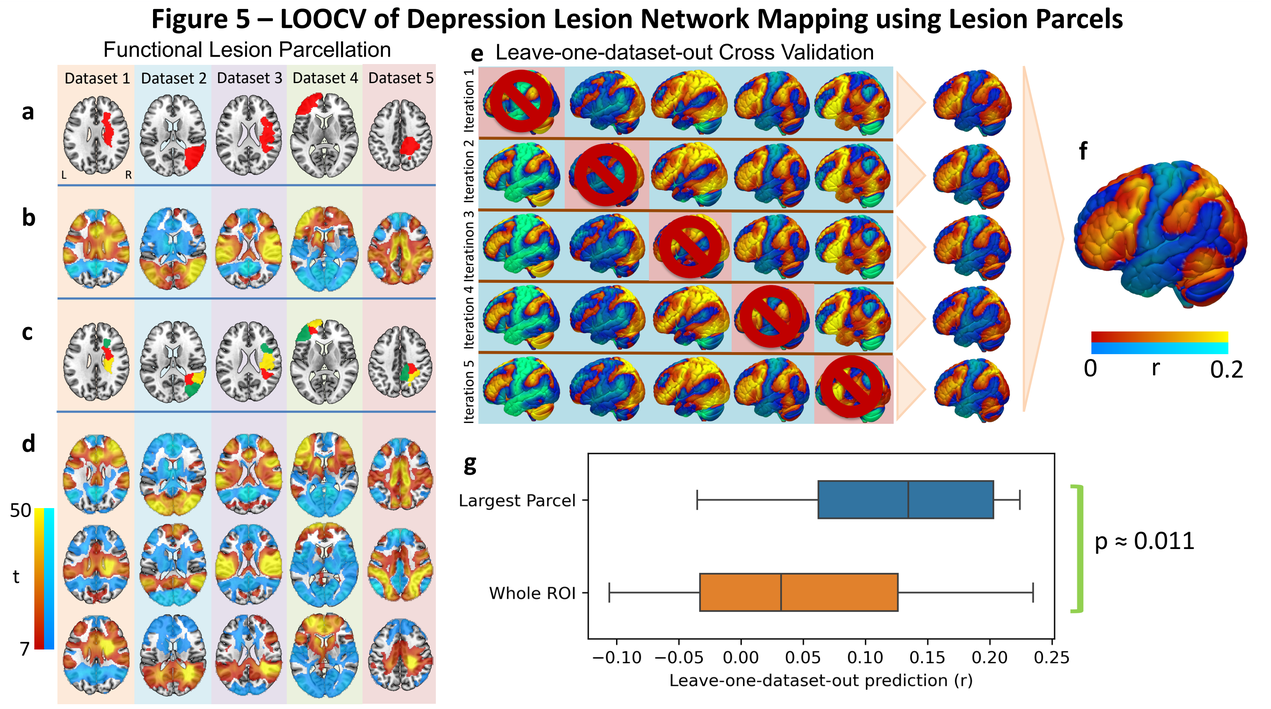
- Functional connectivity maps of whole lesions generated using both the precomputed and conventional LNM methods were similar (spatial r=0.997) and were **far more efficiently computed (~7X faster)** when using a 1,000-subject normative functional connectome.
- In a leave-one-dataset-out cross-validation, lesion network maps derived from the largest parcel of each lesion from four datasets **predicted depression outcomes in the fifth (r=0.155, p<0.001).** This was **significantly stronger (p=0.0011)** than the predictive value of whole lesions.

Figure 4 – Precomputed LNM Benchmarks



(**a**) Lesion connectivity maps computed using the Timecourse lesion network mapping method and the Precomputed lesion network mapping method generated from the same lesion ROI. (**b**) Across a test dataset of stroke lesions (n=135), lesion connectivity maps were computed using both Timecourse and Precomputed lesion network mapping methods. Consistently high spatial correlations between each pair of lesion connectivity maps demonstrate that connectivity maps generated using both methods are very similar (mean r = 0.997, s.d. = 0.004). (**c**) Computation time to generate lesion connectivity maps using both lesion network mapping methods for the test lesion dataset was recorded. Compute times confirmed that the Precomputed lesion network mapping method is approximately seven times faster than the Timecourse lesion network mapping method when using a connectome of 1,000 subjects. Compute time of the Precomputed lesion network mapping method stayed constant with connectome size, while compute time of the Timecourse lesion network mapping method increased linearly.

Figure 5 – LOOCV of Depression Lesion Network Mapping using Lesion Parcels



(a) Stroke lesions from the five lesion datasets each have distinct functional connectivity profiles **(b)**. These stroke lesions can be parcellated using Infomap into functionally distinct parcels **(c)** that each have distinct functional connectivity profiles **(d).** Lesion network mapping is performed using each lesion's largest functional parcel as determined by Infomap. A Leave-One-Dataset-Out Cross Validation is performed, using lesion connectivity data from four datasets to explain variance in the fifth dataset. **(f)** A weighted average of the five "depression network maps" is computed to represent the overall depression functional network map. **(g)** In a leave-one-dataset-out cross-validation, lesion network maps derived from the largest parcel of each lesion from four datasets predicted depression outcomes in the fifth (r=0.155, p<0.001). This was significantly stronger (p ≈ 0.0011) than the predictive value of whole lesions.

Conclusions

- We developed the **precomputed human brain connectome**, a high-resolution atlas of voxel-wise functional connectivity.
- **The precomputed method enables computationally efficient LNM**, even for large connectome datasets.
- **Functionally parcellating lesions improves lesion-symptom localization** when using each lesion's largest isolated parcel compared to whole lesions.
- If lesion-symptom localization can be improved even when using a simple size metric to pick the optimal parcel, **we hypothesize that further improvements in LNM can be achieved by using a more specialized parcel selection method** that could include selecting multiple relevant lesion parcels to consider their interacting network effects.

References

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william.drew100@gmail.com
@WilliamDrew_1
thewilliamdrew

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