How cortical activity co-fluctuations shape neurovascular function in mice

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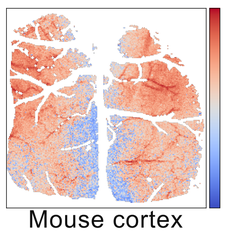
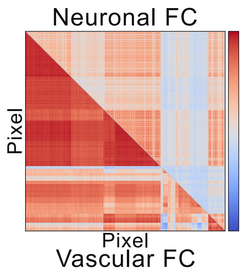
Objectives

Recent research has shown that, in human BOLD fMRI data, **resting state functional connectivity is closely approximated by a small subset of high-amplitude co-fluctuation events** [1]. We validate whether this conclusion can be extended to mice data obtained from wide-field calcium imaging. In addition, we **investigate how those periods of high co-fluctuation events affect the interaction between neuronal and vascular signals**. We thus define:



Neurovascular coupling as the correlation between pixel-wise vascular and neuronal time series.

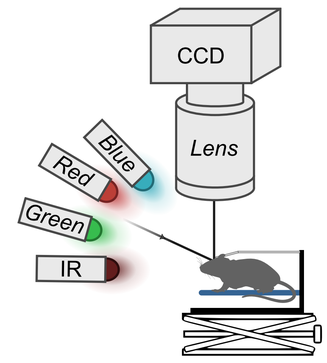


Functional similarity as the correlation between neuronal and vascular functional connectivity matrices.

Animal model and optical imaging

Long-term cranial window and field of view

We use CaMKII-tTa/TRE-GCaMP6s transgenic mice equipped with a long-term cranial window. A wide-field optical imaging system is used to measure **calcium activity (neuronal)** as well as **hemodynamic activity (vascular)** [2].

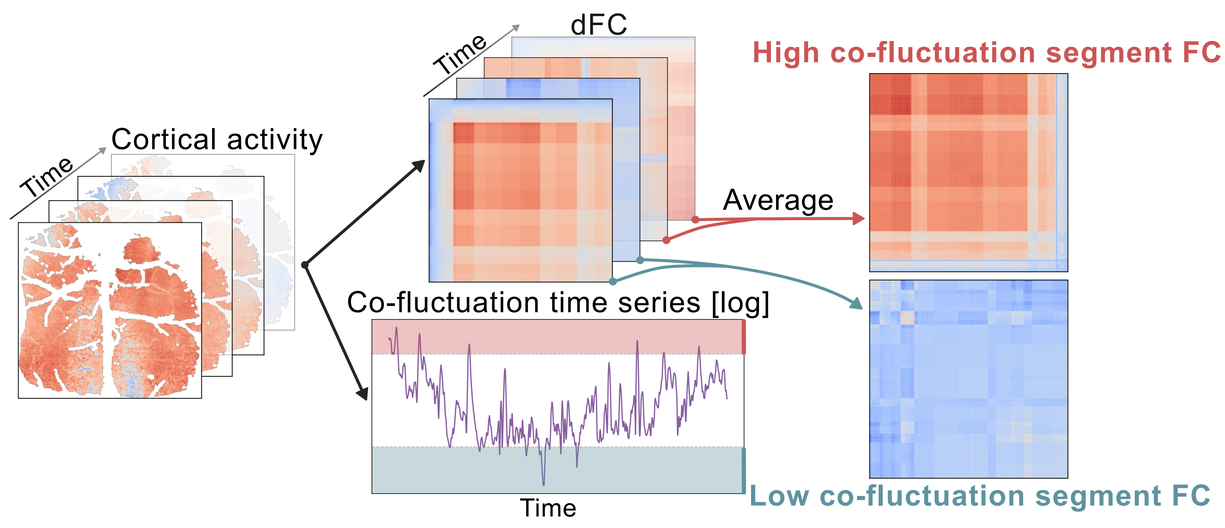


Segments of functional connectivity

Functional connectivity (FC) quantifies the relationship between the activity of different brain regions. It is typically calculated as the temporal average of the **co-fluctuation time series**, which correspond to the element-wise product of z-scored time series. FC provides a summary of network interactions over the entire imaging session.

To explore how FC changes over time and how it relates to neurovascular events, we compute **dynamic functional connectivity (dFC)** at single-frame resolution: at each imaging time point, an FC matrix is generated without temporal averaging. This captures moment-to-moment fluctuations in network function.

We then group dFC matrices according to specific criteria—such as the amplitude of cortical co-fluctuations, arousal, behavior, or external stimuli—to form **functional connectivity segments** [1]. Each segment represents the average FC across non-contiguous time points that share similar network states. This approach reveals how functional connectivity dynamically varies across different levels of brain activity and arousal.



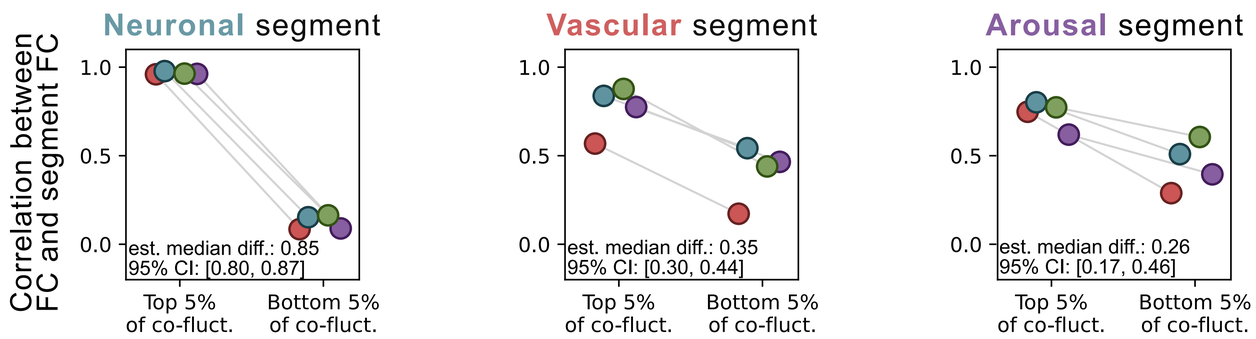
Results validation

Resting-state functional connectivity (FC) is well-approximated by a small subset of dynamic FC (dFC) frames associated with high co-fluctuations [1].

• In four mice, FC segments from the top 5% of co-fluctuations (left) showed higher correlation with full resting-state FC than the bottom 5% (right).

• This effect was consistent across **neuronal** and **vascular** data.

• This effect was also found in neuronal data segmented by **arousal** (via pupil diameter).



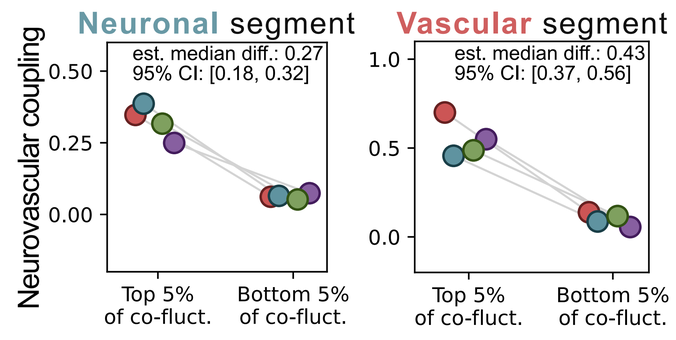
A one-sided bootstrap test on the median of these differences (1,000 resamples with replacement) confirmed the robustness of this effect (p<0.001). The estimated median difference and 95% confidence interval are indicated on the figures.

Co-fluctuations shape neurovascular function

Neurovascular coupling is higher during periods of high co-fluctuations

• In four mice, **neurovascular coupling** was higher when considering the top 5% of co-fluctuations rather than the lowest 5%

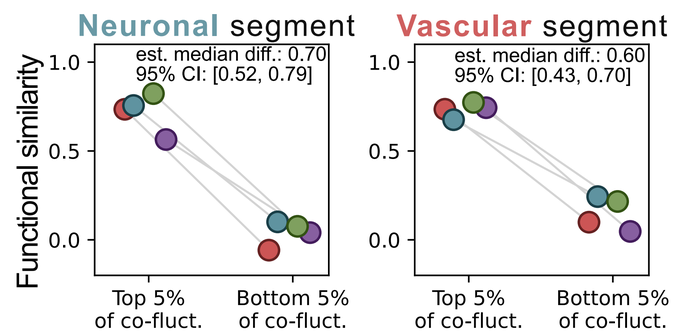
• This effect was larger when considering **vascular** segments rather than **neuronal** segments.



Functional similarity is higher during periods of high co-fluctuations

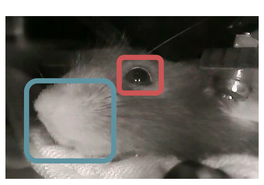
• In four mice, **functional similarity** was higher when considering the top 5% of co-fluctuations rather than the lowest 5%

• This effect was larger when considering **neuronal** segments rather than **vascular** segments.



p<0.001 with a one-sided bootstrap test for all figures above.

Future directions



• Recent research has shown that the neurovascular coupling varies according to the animal's arousal state [3]. By computing the mice's pupil diameter and facial movement as a proxy for arousal, we can employ these measurements to segment time series according to arousal and validate those results.

• Mice are currently being imaged from 6 to 20 months of age. Repeating resting state measurements along with behavioral tests will allow us to analyze the data to better understand the impacts of aging on neurovascular function.

References

[1] F. Zamani Esfahlani et al., "High-amplitude cofluctuations in cortical activity drive functional connectivity", Proceedings of the National Academy of Sciences, 117 (2020) 28393

[2] Y. Ma et al., "Wide-field optical mapping of neural activity and brain haemodynamics: considerations and novel approaches", Philosophical Transactions of the Royal Society B: Biological Sciences, 371 (2016) 20150360

[3] B. C. Rauscher et al., "Neurovascular Impulse Response Function (IRF) during spontaneous activity differentially reflects intrinsic neuromodulation across cortical regions", preprint (2024)