Clusters structure spontaneous activity in presynaptic networks but not randomly sampled neurons

Summary. Our visual perception of the world around us emerges from rich interactions within networks of synaptically connected neurons, each neuron along the visual pathway only accesses information on stimuli encoded by its presynaptic network. However, it is unclear how neurons within a given presynaptic network collectively convey information, as a majority of previous studies on neural coding have randomly sampled subsets of neurons in a region. To address this issue, we monitored neuronal activity within the specific presynaptic neurons providing input to the same neuron in mouse primary visual cortex layer 4 by combining single-cell-initiated transsynaptic tracing with GCaMP6s-expressing rabies viruses and high-speed 3D 2-photon imaging. We find that while pairwise correlations can convey a range of statistical properties of spontaneous activity in randomly sampled neuronal populations, spontaneous activity among presynaptic networks is better captured by higher-order interactions. In particular, high-order interactions are found to be organised into clusters of co-active neurons within each presynaptic network. To investigate whether clusters defined from spontaneous activity are functionally relevant, we inspect the light-evoked responses from neurons within the same cluster. Spontaneous and evoked neural correlations appear aligned in randomly sampled neurons, but depart from each other in presynaptic networks. Our results highlight fundamental differences in neural correlation structure in presynaptic networks and randomly sampled cells, where presynaptic activity is described in terms of clusters defined by higher-order interactions among neurons.

Significance. Though population coding in the brain must rely on the intricate structure of synaptic connectivity, most previous studies have approached population coding by investigating ensembles of randomly sampled neurons within any given brain region. In this work, for the first time, we investigate how neurons in layer 4 of mouse primary visual cortex (V1) within the presynaptic network of a same neuron interact to permit the emergence of a population code for visual stimuli. Although pairwise interactions were evidenced to capture a wide array of neural population statistics across species and brain region, including neural recordings in the retina and cortex (Schneidman et al 2006 *Nature*, Tkacik et al 2014 *PLoS CB*, Hamilton et al 2013 *Neuron*, Ferrari et al 2016 *Phys Rev E*, Tavoni et al 2017 *Net Neurosci*, Nghiem et al 2018 *Phys Rev E*, Zanoci et al 2019 *Phys Rev E*) for recordings of randomly sampled neurons, we find that higher-order interactions are needed to describe population statistics of presynaptic networks. Further, while previous work (Tsodyks et al 1999 *Science*, Miller et al 2014 *PNAS*, Carillo-Reid et al 2016 *Science*, Carillo-Reid et al 2019 *Cell*) has highlighted similarities in the correlation structure of neural activity between spontaneous and stimulus evoked conditions in randomly sampled neurons, our results support that in presynaptic networks, neurons within the same spontaneous (in response to a uniformly gray stimulus) cluster appear slightly less correlated in terms of their responses to stimuli (drifting gratings at different speeds) than for randomly sampled neurons. The results suggest that neural correlations depend upon visual stimuli and context especially in presynaptic networks, which can enhance information coding.

Relevance. A number of current studies strived to uncover low-dimensional structure underlying high-dimensional neural recordings. Dimensionality reduction can amount to finding clusters of co-active neurons: this has often been done for neurons with physiological similarities or similar responses to stimuli. On the other hand, recent work has highlighted the importance of how spontaneous activity is organised (Stringer et al 2019 *Science*, Musall et al 2019 *Nature Neuroscience*). Here, we cluster neurons based on spontaneous dynamics and propose an approach to evaluate to what extent clusters play a key role in structuring collective activity. To that purpose, one can use the most generic model that can reproduce neuron-to-cluster statistical dependencies, or equivalently, one needs a model that maximises entropy subject to the constraint of reproducing empirical correlations between each neuron's activity and each cluster's total activity (Fig. 1d). If this model is a good model for the data, it will capture most characteristics of observed activity and therefore reproduce other statistics it was not explicitly constrained to reproduce. We find that empirical statistics are better described by neuron-to-cluster interactions in presynaptic networks than in randomly sampled neurons, which are better described by lower-order pairwise statistics (Fig. 1e-g).

Additional detail. In a MaxEnt model constrained by the mean firing rates and pairwise covariances only (Fig. 1c), the probability of a firing pattern $\boldsymbol{\sigma}$ is $P(\boldsymbol{\sigma}) = \frac{1}{Z}\exp\left(\sum_i^N b_i\sigma_i + \sum_{j\neq i} J_{ij}\sigma_i\sigma_j\right)$ comprising neural bias towards firing b_i tuned to reproduce empirical mean firing rates, and symmetric pairwise couplings J_{ij} tuned to reproduce empirical pairwise covariances. Z is a normalisation constant. In a MaxEnt model considering neuron-to-population interactions only (Fig. 1d), firing pattern probabilities can be written as $P(\boldsymbol{\sigma}) = \frac{1}{Z}\exp\left[\sum_i^N \sum_{l=0}^{n_{clus}} (\sum_{k_l} h_{iK_l}\delta_{k_l}^{K_l})\sigma_i\right]$, with n_{clus} the number of clusters and $K_l(t) = \sum_{i\in l}\sigma_i(t)$ the number of spikes of neurons in cluster l at time t, and Z is a normalization constant (Nghiem et al 2018 *Phys Rev E*). Combining model-selection analyses with other statistical analyses, we find that the cluster model is more appropriate for presynaptic networks, or equivalently cluster-scale interactions are dominant in presynaptic networks, while interactions are lower-order and pairwise in randomly sampled cells (Fig. 1e). Indeed empirical pairwise correlations are better reproduced by the cluster model in presynaptic compared to randomly sampled neurons (Fig. 1f) and the identity of clusters matters more in presynaptic networks since shuffling cluster labels increase model error up to 6 times (Fig. 1g). Neural responses to drifting grating stimuli are found to be less correlated within clusters defined from spontaneous activity, compared to chance, in presynaptic data (Fig. 1h). Conversely, within the larger clusters obtained from light-evoked responses, spontaneous activity in pairs of presynaptic neurons exhibits weaker correlation than in pairs of randomly sampled neurons (Fig. 1i).

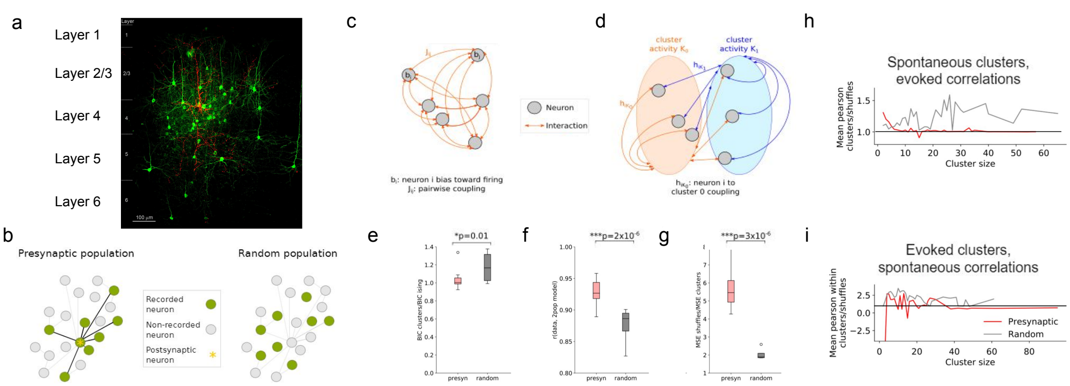

Figure 1: (a) Single-cell-initiated monosynaptic tracing from individual layer 4 neurons in mouse primary visual cortex. Immunostained confocal image from coronal brain slice showing the starter cell (red), its local presynaptic inputs in primary visual cortex (green). (b) Presynaptic network (left) and randomly sampled neurons (right) schematic diagrams. (c-d) MaxEnt models constrained to reproduce pairwise correlations (c) and neuron-to-cluster correlations (d). (e-g) Model performance metrics for presynaptic (red) and randomly sampled neurons (grey), comprising (e) Bayesian Information Criterion ratio between pairwise and cluster models, describing how well population activity patterns are reproduced and showing pairwise interactions only dominate in random cell samples, (f) Pearson correlation between experimental and cluster-model-predicted pairwise covariances, supporting that cluster models more accurately describe presynaptic networks, and (g) Ratio between Mean Square Error (MSE) on pairwise covariance prediction from cluster model and MSE upon shuffling cluster labels, highlighting cluster identities matter 3-4 times more for presynaptic neurons. (h) Mean pairwise correlations between neural responses to stimuli (averaged over time and trials) for neurons within the same cluster defined from spontaneous activity, divided by same quantity for shuffled clusters. (i) Mean pairwise correlations between neural spontaneous activity traces for neurons within the same cluster defined from stimulus responses, divided by same quantity for shuffled clusters. The results suggest cells in the same cluster defined from spontaneous activity are less correlated in terms of responses in presynaptic than random data and vice versa.