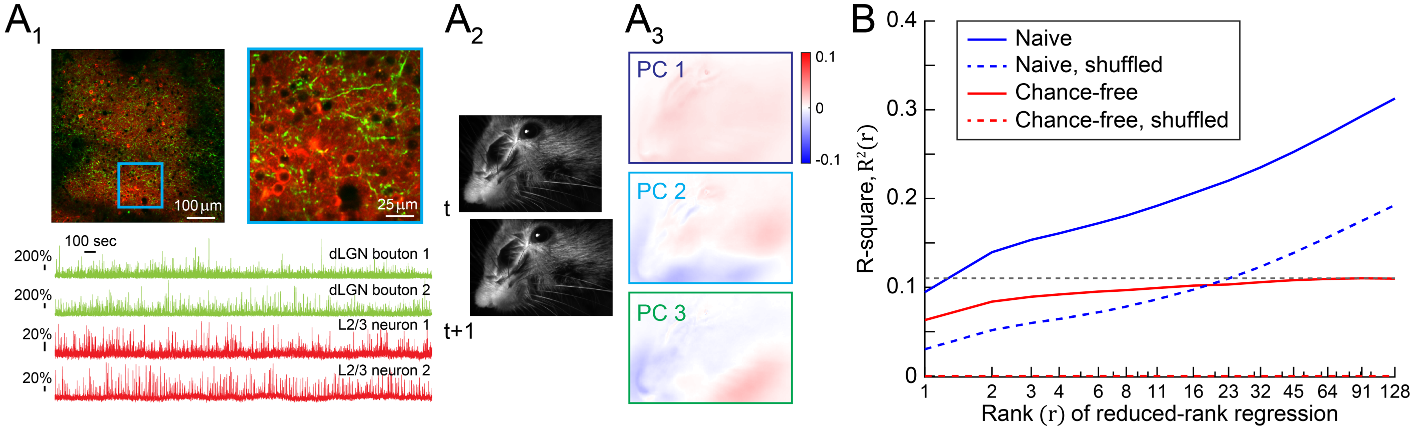
Integration of behavioral related correlation from top-down and bottom-up pathways in mouse V1

Summary

Brain-wide neuromodulation by behavioral variables, such as locomotion, pupil area, and face motion, have been observed in mice (Stringer et al., 2019; Musall et al., 2019). To study this mechanism at higher spatial resolution, we used two-photon imaging that allows recording of individual neuronal and synaptic bouton activity in mouse primary visual cortex (V1), while the animal's face was simultaneously videotaped. We aim to understand how facial motion is related to the population activity of cortical neurons and their lateral geniculate nucleus (LGN) afferents, both during spontaneous and stimuli evoked periods. To avoid spurious correlations due to overfitting from naive linear regression analysis, we applied a variant of ridge regression analysis, where its regularization hyperparameter is optimized to minimize the correlation between facial motion and neuron/bouton activity after random trial permutations. We observed a robust correlation between facial motion and neuronal population activity, which is higher for visually evoked response compared to spontaneous activity. In contrast, LGN bouton activity does not correlate with facial motion during spontaneous periods, but surprisingly becomes significantly correlated for visually evoked responses. To explain this last observation we show that LGN boutons are almost silent during the spontaneous period, in contrast to their high activity during evoked states, implying that the LGN is subthreshold during the spontaneous period and cannot transfer any received information about facial motion. This prompts the hypothesis that the improved encoding of facial motion variables in V1 cortical neurons when visually evoked is mainly due to the onset of facial motion correlated bottom-up visually evoked LGN inputs, rather than stronger top-down movement-related cortical inputs. In total, our work gives an unprecedented analysis of the circuit pathways that underlie the recent observations that mouse V1 activity is related, in part, to non-visual inputs.

Additional Details

We used two-photon imaging to record the activity of cortical neurons and LGN boutons in layer (L) 2/3 and L4 of V1 from awake, head-fixed mice (Figure A_1, red and green respectively in L2/3), during spontaneous and visually evoked periods (in response to sinusoidal drifting gratings). Animal's face motion was recorded simultaneously (Figure A_2). To correlate facial motion and population activity of cortical neurons or LGN afferents, a linear regression model was used, $\mathbf{Y} = \mathbf{AX}$, where $\mathbf{Y}$ is the matrix of $\Delta F/F_0$ of each neuron/bouton over $1000 \sim 3000$ trials that binned at $250 \sim 400$ ms resolution; $\mathbf{X}$ is the matrix of the projection of facial motion onto a set of 500-dimensional 'eigenfaces' that captures the most prominent components of face motion (Figure A_3, first three principal components) (Stringer et al., 2019), and $\mathbf{A}$ is the linear mapping between $\mathbf{X}$ and $\mathbf{Y}$.



The ordinary least-squares solution of $\mathbf{A}$ is given by:

$$\hat{\mathbf{A}} = \mathbf{Y}\mathbf{X}^T(\mathbf{X}\mathbf{X}^T)^{-1} \tag{1}$$

However, a naive regression can lead to overfitting and correlations by chance, especially when the number of data samples are limited. This issue is apparent when using randomly permuted trials for the fitting: nonzero correlations are present. To illustrate, the solid and dashed blue curves in Figure B show the R-square of original and shuffled data for an example recording dataset, using reduced-rank regression method (Izenman, 1975). The $R^2(r)$ for shuffled data exposes these spurious correlations, as a nonzero correlation is measured despite the lack of any true relation between $\mathbf{X}$ and trial-shuffled $\mathbf{Y}$. These suprious correlations obscure the ground truth correlation between neuronal/button activity and face motion.

To quantify the ground truth correlation, we used ridge regression:

$$\hat{\mathbf{A}}_{\text{ridge}} = \mathbf{Y}\mathbf{X}^T(\mathbf{X}\mathbf{X}^T + \lambda\mathbf{I})^{-1} \tag{2}$$

where λ is the regularization hyperparameter. To minimize overfitting, we optimize a rank-dependent $\lambda(r)$ so that for each regression rank r, the regression R^2 with hyperparameter $\lambda(r)$ for the shuffled data is 0 (dashed red curve, Figure B). As a result, the R^2 with the same $\lambda(r)$ for the original data represents a chance-free correlation (solid red curve, Figure B). This chance-free $R^2(r)$ no longer keeps increasing over r but saturates to an upper bound at around 64 dimensions, consistent with previous observations that mouse V1 correlates with low-dimensions of behavioral variables (Stringer et al., 2019).

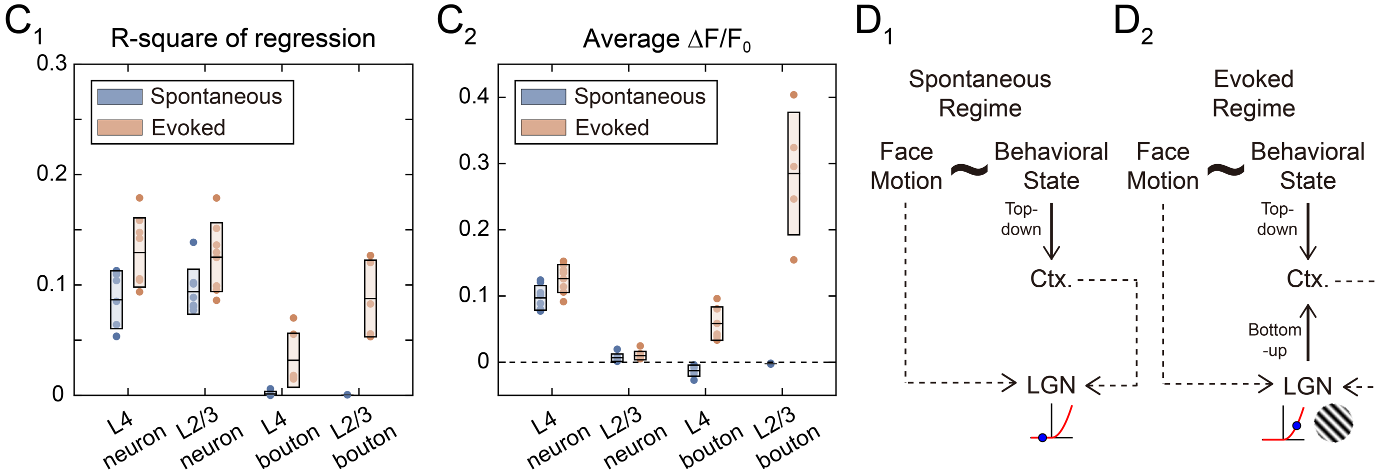


Figure C_1 shows the R^2 statistics for all datasets during both spontaneous and evoked periods (each dot for each recording dataset; bars represent mean and standard deviation). The activity of LGN boutons in L2/3 and L4 are uncorrelated with facial motion in the absence of visual stimuli (spontaneous), but surprisingly become significantly correlated when visually evoked. By contrast, the activity of L2/3 and L4 cortical neurons are correlated with facial motion during both spontaneous and evoked periods, with the correlation being higher in the evoked case.

We conjecture that the correlation between facial motion and V1 activity during spontaneous periods may be due to top-down projections that reflect the behavioral state of the animal (Figure D_1). While the population averaged firing rates of cortical neurons do not show a large change between spontaneous and evoked periods; LGN boutons are almost silent during spontaneous periods, but strongly fire when they are visually evoked (Figure C_2). We thus propose that the increased behavioral correlation for cortical neurons during evoked periods is unlikely due to stronger cortical activity or an increase in the behavioral content of top-down inputs, but rather to the integration of bottom-up LGN inputs that also correlate with behavioral variables, when LGN activity becomes supra-threshold when visually evoked (Figure D_2).

There could be various possible mechanisms for the behavioral correlation within bottom-up inputs, such as the feedback circuitry from the cortical layer 6 back to LGN (Figure D_2, dashed arrow on the right) (Olsen et al., 2012). A non-circuit based mechanism is also possible: the eye motion may increase during visual stimulation, and be highly correlated with face motion (Figure D_2, dashed arrow on the left). Additional experiments such as targeted inhibition in cortical layer 6, or analysis of facial motion that excludes eye motion are required to test these hypotheses.

Interestingly, the correlation of both neuron and bouton populations with behavioral variables is unrelated to the stimulus orientation during the evoked period. Also, facial motion is not sufficient to decode the stimulus orientation better than by chance (results not shown). These observations are consistent with previous studies in mouse V1 suggesting that behavioral variables are encoded on manifolds which are orthogonal to those encoding stimulus orientations (Stringer et al., 2019).