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Interneuron subtypes and orientation tuning

ARISING FROM B. V. Atallah, W. Bruns, M. Carandini & M. Scanziani *Neuron* **73,** 159–170 (2012); N. R. Wilson, C. A. Runyan, F. L. Wang & M. Sur *Nature* **488,** 343–348 (2012); S.-H. Lee *et al. Nature* **488,** 379–383 (2012)

Parvalbumin-positive (PV^+) and somatostatin-positive (SST^+) interneurons are two principal subtypes of cortical GABAergic neurons that differ in morphology, physiological properties and postsynaptic targeting[1–4]. Although GABAergic inhibition is known to be crucial for shaping orientation tuning in the visual cortex[5–7], it is unclear whether PV^+ and SST^+ interneurons have different roles. Recently, Atallah *et al.*[8], Wilson *et al.*[9] and Lee *et al.*[10] addressed this issue by optogenetically manipulating each interneuron subtype, reaching different conclusions: some investigators found that SST^+ neuron activation sharpens orientation tuning[9], whereas PV^+ neuron activation has little effect[8,9], but others found that activation of PV^+ but not SST^+ interneurons sharpens orientation tuning[10]. To understand the cause for the discrepancy we examined the impact of several experimental differences among the studies—anaesthesia and the level and duration of optogenetic stimulation—and found that the discrepancies can be largely explained by differences in the level and duration of interneuron activation. There are replies to this Brief Communication Arising by Atallah, B. V., Scanziani, M. & Carandini, M. *Nature* **508,** http://dx.doi.org/10.1038/nature13129 (2014) and El-Boustani, S., Wilson, N. R., Runyan, C. A. & Sur, M. *Nature* **508,** http://dx.doi.org/10.1038/nature13130 (2014).

Atallah *et al.*[8] showed that mild PV^+ activation caused no significant reduction in orientation tuning width (σ), whereas Lee *et al.*[10] showed that σ reduction is strongly correlated with firing rate reduction (Supplementary Fig. 3e in Lee *et al.*[10]). This indicates that the difference between the findings is related to the degree of PV^+ activation. To test the dependence of σ reduction on the level of interneuron activation further, we measured tuning curves of each neuron in anaesthetized mouse V1 at several light intensities (Fig. 1). For PV^+ activation, both the firing rate and σ decreased progressively with increasing light intensity (Fig. 1a, b). Increasing levels of SST^+ activation, however, caused a progressive reduction of firing rate but not of σ (Fig. 1c, d). The range of PV^+ activation-induced firing rate reduction reported by Atallah *et al.*[8] is indicated by grey shading in Fig. 1b. Within this range we also observed only weak sharpening of orientation tuning, indicating that different levels of PV^+ activation can largely explain the different observations in Lee *et al.*[10] and Atallah *et al.*[8]. Mechanistically, subtractive inhibition by PV^+ activation (Fig. 3 in ref. 10) is considered to be the main cause for the sharpening: stronger PV^+ activation causes a greater increase of spike threshold and therefore stronger firing reduction and sharpening.

However, the discrepancy between the findings of Lee *et al.*[10] and Wilson *et al.*[9] is more profound, and there are two major experimental differences: choice of anaesthetics and laser stimulus duration. As shown in Fig. 2a–e, the specific effect of PV^+ activation on σ reduction was also found in awake, head-fixed mice, indicating that it is not restricted to particular anaesthesia. Meanwhile, in each trial of visual stimulation (4 s), Wilson *et al.*[9] applied 1 s of laser simulation at the beginning of visual stimuli, whereas Lee *et al.*[10] applied laser stimulation throughout the 4 s. To test the effect of laser duration, we measured tuning with 1-s laser stimulation in awake PV-channelrhodopsin-2 (ChR2) and SST-ChR2 mice. In both cases, neuronal firing was reduced only during the 1 s of laser stimulation (Fig. 2f, h). In PV-ChR2 mice, 1-s stimulation caused no significant sharpening of tuning, whereas in SST-ChR2 mice it caused a significant sharpening (Fig. 2f–j).

The lack of sharpening with 1-s PV^+ activation is not unexpected given that inhibition was enhanced only during 1 out of 4 s of visual stimulation (Fig. 2f). However, the sharpening by 1 s but not 4 s of SST^+ activation was unexpected. Notably, during the last 3 s of visual stimulation we observed significant σ reduction with 1-s ($P = 0.003$) but not 4-s ($P = 0.47$) SST^+ activation. One possibility is that whereas the 1-s SST^+ activation caused inhibition of PV^+ neurons[11,12], the laser offset caused rebound activity of PV^+ neurons, which in turn caused σ reduction after laser offset.

Finally, we performed cell-attached recordings from genetically labelled cell types without ChR2 stimulation. Pyramidal, PV^+ and SST^+ neurons all exhibited sustained responses to visual stimulation with similar time courses (Fig. 2k), suggesting that both PV^+ and SST^+ neurons are naturally co-active with pyramidal neurons during visual stimulation. Future studies are necessary to understand fully how different spatiotemporal patterns of PV^+ and SST^+ neuron activation affect visual cortical processing, as simultaneous activation or silencing of all neurons belonging to a particular subtype is still a relatively crude manipulation. Nevertheless, these results indicate that the discrepancy between Lee *et al.*[10] and Wilson *et al.*[9] can be largely explained by different durations of optogenetic activation.

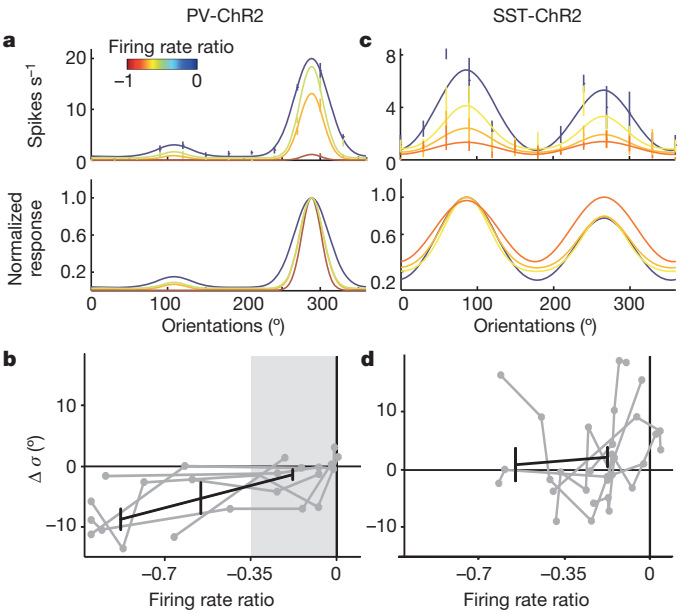

Figure 1 | Correlation between σ reduction and firing rate reduction. **a**, **b**, Juxtacellular recording from putative pyramidal neurons in anaesthetized PV-ChR2 mice showed that σ is reduced progressively with increasing levels of PV^+ neuron activation and pyramidal neuron firing rate reduction. **a**, Top: tuning curves of an example neuron at different levels of optogenetic activation; blue to red, firing rate ratio from 0 to −1; error bars indicate s.e.m.; curve, Gaussian fit of the data. Bottom: tuning curves of the same neuron, each normalized by its peak firing rate. **b**, Change of σ versus firing rate ratio. Each grey line represents a single cell; black line, average $\Delta\sigma$ within three ranges of firing rate ratio (0 to −0.35), (−0.35 to −0.7) and (−0.7 to −1). Error bars indicate s.e.m. ($n = 8$ cells); grey shading, range of firing rate ratios reported by Atallah *et al.*[8]. **c**, **d**, Similar to **a**, **b**, but for SST-ChR2 mice ($n = 8$).

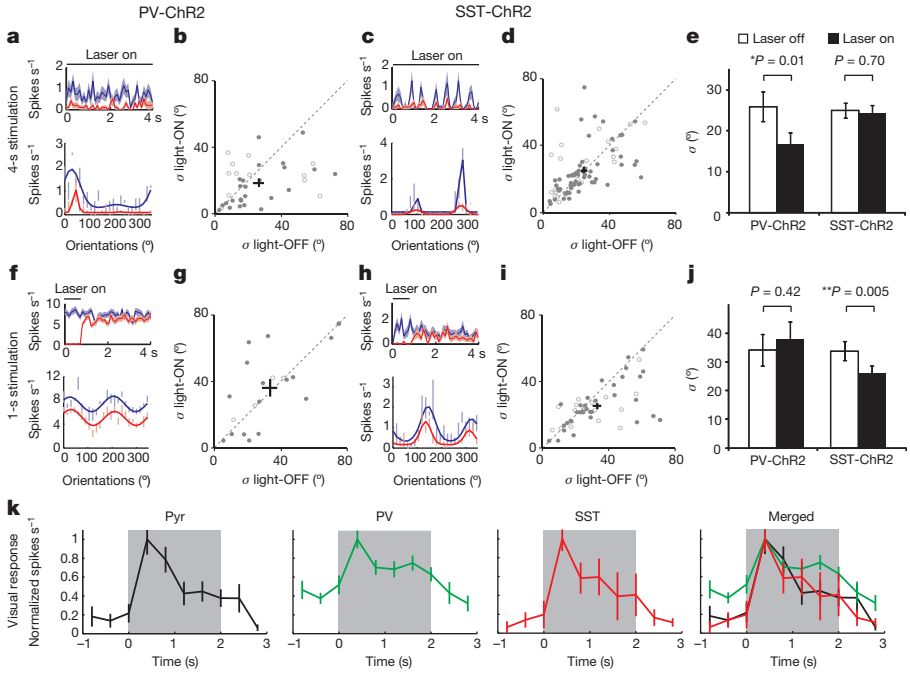

Figure 2 | Effects of 1-s and 4-s laser stimulation on σ in awake PV-ChR2 and SST-ChR2 mice. **a**–**e**, 4-s activation of PV^+ but not SST^+ neurons sharpened orientation tuning. **a**, An example neuron in a PV-ChR2 mouse. Top: firing rates with (red) and without (blue) laser stimulation. Shading indicates s.e.m. Bottom: tuning curves of the same cell with (red) and without (blue) laser stimulation; vertical lines indicate firing rate at each orientation, mean ± s.e.m. **b**, Population summary of σ in PV-ChR2 mice ($n = 37$ cells). Filled circles, cells with firing rate ratio <0; open circles, cells with firing rate ratio >0; black cross, mean ± s.e.m. of the population. **c**, **d**, Similar to **a**, **b**, but for SST-ChR2 mice ($n = 81$). **e**, Mean σ across each population of neurons with (black) and without (white) light stimulation (only cells with firing rate ratio <0 were included). Error bars indicate s.e.m. **f**–**j**, Similar to **a**–**e**, but with 1-s laser stimulation at the beginning of each trial. PV-ChR2, $n = 21$; SST-ChR2, $n = 49$. **k**, Time course of visually driven responses of pyramidal ($n = 15$), PV^+ ($n = 18$) and SST^+ ($n = 4$) neurons in anaesthetized mice. The response of each neuron was normalized by its peak firing rate and averaged across cells. Grey shading indicates period of visual stimulation. Error bars indicate s.e.m.

Methods

PV-Cre or SST-Cre mice were injected with AAV2/2 for ChR2 expression and implanted with head plates 2–3 weeks before recording. All procedures were approved by Animal Care and Use Committee at UC Berkeley. In anaesthetized mice (PV-ChR2, $n = 8$ mice; SST-ChR2, $n = 8$), juxtacellular recording was made under a two-photon microscope, and optogenetic stimulation was made with LED through the objective. In awake mice (PV-ChR2, $n = 25$; SST-ChR2, $n = 21$), recording was made with multichannel silicon probes. Visual stimulation, optogenetic activation and data analysis followed ref. 10. Tuning width change was measured by $\sigma_{\text{light-ON}} - \sigma_{\text{light-OFF}}$. Firing rate ratio was measured during visual stimulation as (firing $\text{rate}_{\text{light-ON}}$ − firing $\text{rate}_{\text{light-OFF}}$)/(firing $\text{rate}_{\text{light-ON}}$ + firing $\text{rate}_{\text{light-OFF}}$).

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1. Markram, H. *et al.* Interneurons of the neocortical inhibitory system. *Nature Rev. Neurosci.* **5,** 793–807 (2004).
2. Ascoli, G. A. *et al.* Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. *Nature Rev. Neurosci.* **9,** 557–568 (2008).
3. Xu, X., Roby, K. D. & Callaway, E. M. Immunochemical characterization of inhibitory mouse cortical neurons: three chemically distinct classes of inhibitory cells. *J. Comp. Neurol.* **518,** 389–404 (2010).
4. Fishell, G. & Rudy, B. Mechanisms of inhibition within the telencephalon: "where the Wild Things are". *Annu. Rev. Neurosci.* **34,** 535–567 (2011).
5. Sillito, A. M. Inhibitory mechanisms influencing complex cell orientation selectivity and their modification at high resting discharge levels. *J. Physiol. (Lond.)* **289,** 33–53 (1979).
6. Nelson, S., Toth, L., Sheth, B. & Sur, M. Orientation selectivity of cortical neurons during intracellular blockade of inhibition. *Science* **265,** 774–777 (1994).
7. Katzner, S., Busse, L. & Carandini, M. $GABA_A$ inhibition controls response gain in visual cortex. *J. Neurosci.* **31,** 5931–5941 (2011).
8. Atallah, B. V., Bruns, W., Carandini, M. & Scanziani, M. Parvalbumin-expressing interneurons linearly transform cortical responses to visual stimuli. *Neuron* **73,** 159–170 (2012).
9. Wilson, N. R., Runyan, C. A., Wang, F. L. & Sur, M. Division and subtraction by distinct cortical inhibitory networks *in vivo*. *Nature* **488,** 343–348 (2012).
10. Lee, S.-H. *et al.* Activation of specific interneurons improves V1 feature selectivity and visual perception. *Nature* **488,** 379–383 (2012).
11. Xu, H., Jeong, H.-Y., Tremblay, R. & Rudy, B. Neocortical somatostatin-expressing GABAergic interneurons disinhibit the thalamorecipient layer 4. *Neuron* **77,** 155–167 (2013).
12. Pfeffer, C. K., Xue, M., He, M., Huang, Z. J. & Scanziani, M. Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. *Nature Neurosci.* **16,** 1068–1076 (2013).

Author Contributions S.-H.L. and Y.D. conceived and designed the experiments. S.-H.L. and A.C.K. performed experiments. S.-H.L., A.C.K. and Y.D. analysed the data. S.-H.L. and Y.D. wrote the manuscript.

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Atallah *et al.* reply

REPLYING TO S.-H. Lee, A. C. Kwan & Y. Dan *Nature* **508,** http://dx.doi.org/10.1038/nature13128 (2014)

Solving discrepancies in the literature is critical for the advancement of science, and the Comment by Lee *et al.*[1] is thus welcome. It clarifies that there is no contradiction between the earlier study of Lee *et al.*[2] and our study[3]. The disagreement is in the interpretation of the results and in the model used to fit the data.

Both studies[2,3] optogenetically perturbed the activity of inhibitory parvalbumin-expressing (PV^+) cells in mouse visual cortex and measured the resulting impact on the orientation tuning width of pyramidal cells. Whereas Lee *et al.*[2] reported a narrowing of the tuning width, our study[3] did not observe any systematic change.

The most obvious effect on photoactivation of PV^+ cells is the reduction in the firing of pyramidal cells. Accordingly, we are glad that when Lee *et al.*[1] (see accompanying Comment) consider the same range of pyramidal cell firing reduction as that described in our study[3] (that is, up to ~50% reduction, for a ratio of −0.34), there is no narrowing of the tuning curve. This narrowing, on the other hand, is present when exploring larger reductions in pyramidal cell firing, consistent with the findings of Lee *et al.*[2].

These effects can be explained by the simple linear model with threshold proposed by our study[3]. In this model, the impact of PV^+ cells is to subtract and scale orientation tuning curves, unless the firing rate is 0. The model captures not only the data in our study[3], but also the data points of the example cell shown in figure 1 of the Comment[1]. As illustrated in our Fig. 1, this model fits the data very well, so all these results can be explained by a simple 'iceberg effect'.

Moreover, the model explains additional data obtained by our study[3], which are not mentioned in the Comment[1]. Our study[3] performed the reverse experiment, namely the optogenetic suppression of PV^+ cells to increase pyramidal cell firing rate up to 250%, and again found that there was no systematic increase in tuning width. As described in our study[3], the model explains this finding because once the iceberg is out of the water it cannot get wider by rising further.

Therefore, one can fully reconcile Lee *et al.*[2] and our study[3] by pointing out (1) that when one explores both intermediate and large reductions in pyramidal cell firing rates one sees both effects (invariance and narrowing of tuning width, respectively, as the Comment does[1]); and (2) that when one uses the linear-threshold model[3] one explains all of these effects. We believe that interpreting the data in the context of such a model is superior to comparing Gaussian functions fit to responses obtained with and without stimulation, as was done in Lee *et al.*[2]. It is closer to the biological reality of a spike threshold, more parsimonious, and therefore more informative as to the functional effect of PV^+ cells on pyramidal cells.

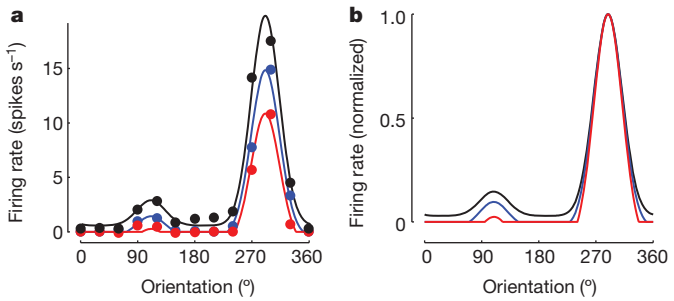

Figure 1 | The linear-threshold model captures the effects of increasing PV activation. **a**, Responses of a pyramidal cell to stimuli of different orientations, in control conditions (black) or in the presence of increasing PV cell activation (blue, moderate PV cell activation; red, stronger PV cell activation). The data are the same of those in figure 1 of Lee *et al.*[1], and were obtained with the Matlab function 'grabit.m'. We did not consider a fourth set of points, with the lowest firing rate, as there are barely any data points above zero. The curves indicate the fits of the linear-threshold model introduced by our study[3]. **b**, The same curves as in **a**, rescaled to peak at 1, to illustrate a mild but progressive narrowing of tuning curves with increasing PV^+ cell activation.

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1. Lee, S.-H., Kwan, A. C. & Dan, Y. Interneuron subtypes and orientation tuning. *Nature* **508,** http://dx.doi.org/10.1038/nature13128 (2014).
2. Lee, S.-H. *et al.* Activation of specific interneurons improves V1 feature selectivity and visual perception. *Nature* **488,** 379–383 (2012).
3. Atallah, B. V., Bruns, W., Carandini, M. & Scanziani, M. Parvalbumin-expressing interneurons linearly transform cortical responses to visual stimuli. *Neuron* **73,** 159–170 (2012).

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El-Boustani *et al.* reply

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Several recent studies have examined the function of parvalbumin-expressing (PV^+) and somatostatin-expressing (SST^+) inhibitory neurons in V1 (refs 1–3). Although it is commonly agreed that these cell types alter the responses of pyramidal neurons in distinct ways—via divisive or subtractive inhibition—their specific roles remain a matter of debate. The Comment by Lee *et al.*[4] presents new data suggesting that the differences between the results of Lee *et al.*[2] compared to Atallah *et al.*[3] and Wilson *et al.*[1] could be explained by the strength and duration of laser stimulation used to optogenetically activate these two classes of inhibitory neuron. The data presented by Lee *et al.*[4] now clarify that PV^+ neurons, when probed with small amounts of optogenetic activation, do not significantly change the tuning of their target cells, confirming Atallah *et al.*[3] and Wilson *et al.*[1]. The new SST^+ results presented in the Comment[4] show that SST^+ neurons can subtract responses, consistent with Wilson *et al.*[1], but we suggest that the switch of function of SST^+ neurons in their data between short (1 s) and long (4–5 s) stimulation reveals a core principle of inhibition in cortical networks rather than simply being a peculiarity of stimulation protocols.

The fundamental difference between these two conditions resides in the temporal overlap between inhibitory neuron activation and target-cell responses: when these overlap, inhibition is divisive (causing no change in tuning width of target neurons), but when they do not overlap, inhibition is subtractive (and reduces tuning width).

Lee *et al.*[2] found that activation of PV^+ neurons can reduce the orientation tuning width of target neurons, whereas Atallah *et al.*[3] and Wilson *et al.*[1] reported a divisive effect, mainly resulting in scaling down the orientation tuning curve without significant changes of tuning width. If PV^+ neurons are strongly stimulated with channelrhodopsin-2 (ChR2) by increasing the laser intensity or duration, they can markedly reduce pyramidal neuron responses and narrow their tuning widths, as explicitly noted by Wilson *et al.* (see Supplementary Figs 6 and 7 of ref. 1)—both Wilson *et al.*[1] and Atallah *et al.*[3] used only moderate amounts of PV^+ activation to avoid the 'floor effect' on target neurons. The new data presented by Lee *et al.*[4] (see Fig. 1) now show that moderate stimulation of PV^+ neurons does not result in substantial tuning width reduction, similar to the findings reported by Atallah *et al.*[3] and Wilson *et al.*[1]. However, in this stimulation intensity range, they do not report any gain modulation of target cell responses as observed by Wilson *et al.*[1] and Atallah *et al.*[3]. This discrepancy, as well as the nature of the effect observed in the new data presented by Lee *et al.*[4], remains to be clarified.

Regarding SST^+ neurons, both Wilson *et al.*[1] and the new data presented by Lee *et al.*[4] show that the effect of these neurons on target cells as measured after 1 s of laser stimulation is subtractive. This is in contrast to the divisive effect found by Lee *et al.*[2] when SST^+ neurons were stimulated during the entire duration of visual stimulation. Lee *et al.*[4] suggest that the new findings may be explained by SST^+ to PV^+ inhibition and rebound of PV^+ neuron activity after laser offset. We believe that this is unlikely, as direct (presumably stronger) activation of PV^+ inhibition by 1 s of laser stimulation was not strong enough to reduce the tuning width, as reported by Wilson *et al.*[1] and now by Lee *et al.*[4].

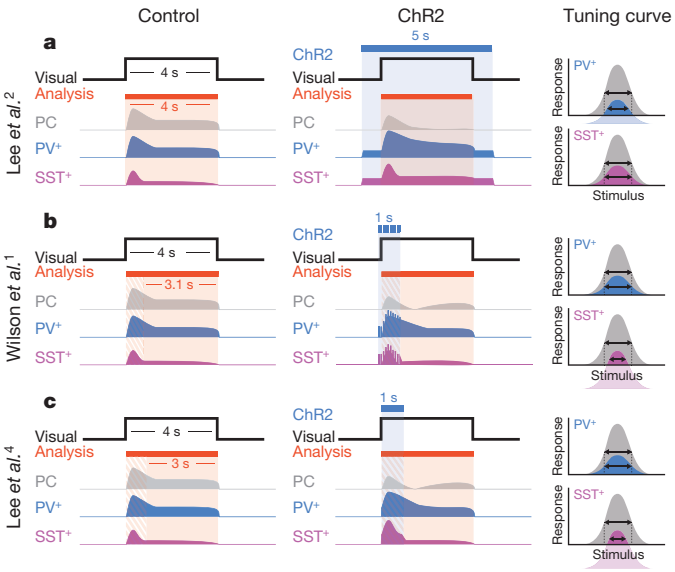

Figure 1 | Schematic of the different experimental protocols used in Lee *et al.*[2], Wilson *et al.*[1] and Lee *et al.*[4]. **a**–**c**, For each study (**a**, Lee *et al.*[2]; **b**, Wilson *et al.*[1]; **c**, Lee *et al.*[4] (accompanying Comment)), the left panel describes the control protocol where neuron activity is recorded during visual stimulation alone from pyramidal cells (PC), parvalbumin-expressing cells (PV^+) and somatostatin-expressing cells (SST^+); the middle panel describes the same experiment when inhibitory neurons are activated with ChR2; and the right panel shows the resulting effect of ChR2 activation on target cell tuning curves for PV^+ (blue, top) and SST^+ (pink, bottom) neurons. In the protocol description (left and middle panels), the visual stimulus duration (4 s) is indicated in black, the time epoch during which the analysis has been performed (4, 3 or 3.1 s) in red and the duration of ChR2 activation in blue (middle panel). The hatched red area indicates segment of the visual stimulation that was not always included in the analysis. Note that pulses are indicated by single blue lines (**b**) whereas continuous stimulation is indicated by a bar (**a**, **c**). Stereotypical responses of pyramidal neurons (grey) as well as PV^+ (blue) and SST^+ (pink) inhibitory neurons are depicted (left and middle panels), as well as the suggested effect of temporal co-activation on pyramidal neuron tuning width (arrows, right panel).

Instead, we suggest that this result can be explained by the response properties of different inhibitory neurons and their co-activation with target cells. The visual responses of SST^+ neurons are distinct from PV^+ or pyramidal neurons in terms of response latency[5], size tuning curve[6] and correlation with nearby pyramidal cells[7]. Probing the function of inhibitory neurons using visual (as well as ChR2) stimulation invokes these response modes, which shapes their effect on pyramidal cells. Crucially, PV^+ neurons are routinely co-activated with pyramidal neurons by the visual stimuli used to measure tuning; such co-activation (even when ChR2-mediated inhibition is added in small amounts) fundamentally divides pyramidal neuron responses. The inhibition that SST^+ neurons provide is a function of whether or not they are co-activated with target pyramidal neurons by visual stimuli and ChR2 (Fig. 1). Prolonged ChR2 stimulation of SST^+ neurons may force them to be co-active with pyramidal neurons during visual stimulation and the analysis time period (Lee *et al.*[2]), resulting in a divisive effect. Driving these neurons only during the initial segment of visual response, with pulse trains (Wilson *et al.*[1]) or steady stimulation (Lee *et al.*[4]), may reduce the co-activation during the analysis period, resulting in a subtractive effect. More generally, sustained ChR2 activation of inhibitory neuron subtypes is superimposed not only on visual responses of neurons but also on complex inhibitory–disinhibitory circuits[8], making it difficult to resolve clearly the function of these subtypes *in vivo*. As the duration of ChR2-mediated stimulation of specific inhibitory neurons seems to determine the effect on target cells, the use of moderate single-pulse probes of light could reveal the core principles of direct inhibition in functioning visual cortex networks without the risk of fundamentally perturbing the ongoing network dynamics through recurrent inhibitory circuits[9].

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1. Wilson, N. R., Runyan, C. A., Wang, F. L. & Sur, M. Division and subtraction by distinct cortical inhibitory networks *in vivo*. *Nature* **488,** 343–348 (2012).
2. Lee, S.-H. *et al.* Activation of specific interneurons improves V1 feature selectivity and visual perception. *Nature* **488,** 379–383 (2012).
3. Atallah, B. V., Bruns, W., Carandini, M. & Scanziani, M. Parvalbumin-expressing interneurons linearly transform cortical responses to visual stimuli. *Neuron* **73,** 159–170 (2012).
4. Lee, S.-H., Kwan, A. C. & Dan, Y. Interneuron subtypes and orientation tuning. *Nature* **508,** http://dx.doi.org/10.1038/nature13128 (2014).
5. Ma, W. *et al.* Visual representations by cortical somatostatin inhibitory neurons—selective but with weak and delayed responses. *J. Neurosci.* **30,** 14371–14379 (2010).
6. Adesnik, H., Bruns, W., Taniguchi, H., Huang, Z. J. & Scanziani, M. A neural circuit for spatial summation in visual cortex. *Nature* **490,** 226–231 (2012).
7. Gentet, L. J. *et al.* Unique functional properties of somatostatin-expressing GABAergic neurons in mouse barrel cortex. *Nature Neurosci.* **15,** 607–612 (2012).
8. Pfeffer, C. K., Xue, M., He, M., Huang, Z. J. & Scanziani, M. Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. *Nature Neurosci.* **16,** 1068–1076 (2013).
9. Brunel, N. & Hakim, V. Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. *Neural Comput.* **11,** 1621–1671 (1999).

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