

Putting the brakes on synchrony: VIP interneurons tune visually evoked rhythmic activity

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Visually evoked synchrony in the primary visual cortex has proven to be a robust model for examining circuit interactions. In this issue of *Neuron*, Veit et al.¹ highlight a previously unappreciated role for VIP interneurons in regulating local and long-range patterns of coordinated neural activity.

Temporal synchrony of neuronal activity in the cerebral cortex is thought to play an important role in cognition by stabilizing population codes and enhancing information transfer between distant areas. Theoretical and experimental work has shown that robust neuronal synchrony can arise from a wide range of circuit architectures, particularly when GABAergic inhibition gates the multiple sources of synaptic input received by excitatory neurons.² However, mechanisms that might constrain or suppress the synchronization of neural activity in the awake cortex remain poorly understood.

One of the most studied and fiercely debated examples of cortical synchronization was first described in a seminal study by Charles Gray and Wolf Singer in the late 1980s.³ They found a strong synchronization of local field potential (LFP) activity in the gamma range (30–80 Hz) in the upper layers of the visual cortex of anesthetized cats during the display of visual gratings. Most interestingly, they observed synchronization across distant retinotopic sites specifically when they were activated by a common stimulus. This led to the binding hypothesis: the idea that gamma synchronization helps to integrate the visual features of an object across the retinotopic space into a single percept. Long-range visually evoked synchrony was likewise detected in other binocular mammals, such as monkeys and ferrets.⁴ However, the binding hypothesis was eventually challenged by evidence that objects having inhomogeneous color or texture do not elicit gamma synchronization across distant retinotopic sites.⁴ Furthermore, the neuronal mechanisms of visually

evoked long-range synchrony proved difficult to decipher experimentally.

A breakthrough in the study of visually evoked patterned activity recently came from two studies, led, respectively, by Julia Veit in the laboratory of Hillel Adesnik⁵ and Guang Chen in the team of Xiaohui Zhang.⁶ These authors observed that visually evoked synchronization in the gamma range was also present in the visual cortex of mouse, albeit at lower frequencies (~30 Hz). As in cat and monkey, single stimuli with homogeneous visual features evoked synchronization across distant retinotopic sites. Crucially, optogenetic manipulation showed that synchrony in this frequency range requires the activation of a specific class of GABAergic interneuron that co-expresses the peptide somatostatin (SST). These results uncovered novel circuit mechanisms underlying visually evoked gamma synchronization but left a key question unanswered: how is the robust promotion of synchrony by SST neurons dynamically regulated as a function of visual context?

In the current issue of *Neuron*,¹ a new study by Julia Veit, Hillel Adesnik, and coauthors addresses this question and provides surprising insight into a decades-old problem. The cortical network comprises multiple types of GABAergic interneurons, including SST cells and two other classes that co-express parvalbumin (PV) and vasoactive intestinal peptide (VIP), respectively (Figure 1). VIP interneurons strongly inhibit SST interneurons.⁷ Using optogenetic manipulations, the authors found that suppression of VIP interneuron activity resulted in a marked increase in local gamma-range synchronization. Notably, suppressing VIP neurons did not

boost the synchronization typically observed between distant retinotopic sites activated by a common stimulus. However, suppressing VIP neurons revealed synchronization across sites in response to stimuli with different features, suggesting that VIP-SST inhibition normally serves to reduce long-distance synchrony to mismatched stimuli (Figures 1B and 1C).

These elegant results advance the description of visually evoked cortical synchronization and present insightful and unforeseen constraints. They suggest that local circuits are inherently permissive for cortical synchronization during visual processing, regardless of whether stimuli have homogeneous visual features across the retinotopic space. However, this synchrony is selectively squelched by VIP-SST inhibition when visual features are mismatched across sites. VIP interneurons may thus play a unique role in downregulating visually evoked cortico-cortical synchrony. These results also suggest that cortical synchronization may not always be advantageous and may be more tightly regulated in the local circuit than was previously appreciated.

This new view of the local circuit sheds light on previous findings. Theoretical work has found that synchronization arises in networks of excitatory and inhibitory neurons (E-I networks) under a wide range of connectivity constraints and architectures.² Veit et al. make use of a computational modeling framework to illustrate how the addition of a class of inhibitory neurons having some of the properties and connectivity of VIP interneurons can act as a gate to tune synchrony. Their work thus illustrates how the natural synchrony of E-I networks

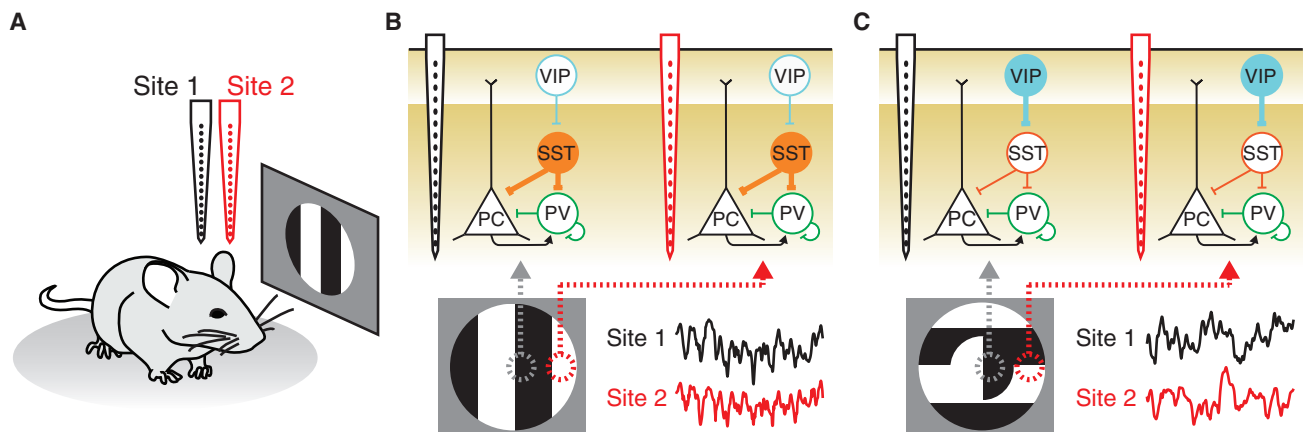


Figure 1. VIP and SST interneurons regulate visually evoked synchrony across retinotopic sites

(A) Veit et al. recorded the LFP, which largely arises from synchronous synaptic currents in the local circuit, at two distinct retinotopic sites in the visual cortex of head-fixed awake mice using silicon probes.

(B) Visually evoked synchrony in the 20–40 Hz range is observed when both sites (black and red, respectively) are activated by a common stimulus having consistent visual features. This synchrony arises from a network architecture involving excitatory, glutamatergic pyramidal cells and inhibitory, GABAergic interneurons that co-express either PV or SST. Synchrony in the low gamma range specifically depends on activation of SST interneurons.

(C) Mismatched visual features across retinotopic sites activate a third population of GABAergic interneurons that co-express VIP. VIP cells specifically inhibit SST cells, disrupting synchrony.

might be exploited and regulated in both theoretical and natural scenarios. Veit et al. also provide a new perspective on the intriguing behavior of VIP interneurons during visual stimulation. Indeed, recent work found that VIP interneurons may be selectively activated by low-contrast stimuli, which are associated with minimal gamma synchronization and are relatively inactive during presentation of highly salient stimuli.⁸ This peculiar tuning could potentially benefit the network by helping to reduce synchrony in a context-dependent manner.

These findings raise several important questions about the potential functional roles of sensory-evoked neural synchrony in the cortex. What is the benefit of visually evoked synchrony? How might unregulated synchrony be detrimental in certain circumstances? Recent work has proposed that synchrony could help compress information when visual scenes present repeating or predictable elements.^{4,9} This theory offers a potential framework for understanding the regulatory role of VIP interneurons. In this model, VIP interneurons would function to adjust the level of compression of the visual code to ensure that low redundancy does not come at the expense of information loss. A closely related question is how synchrony, or the lack thereof, shapes the processing of visual input. In a recent

study,¹⁰ our group found that visually evoked synchrony did not enhance visual encoding in local cortical neurons, but bottom-up visual processing was instead boosted by a different pattern at higher frequencies. Together, these findings are consistent with a role for visually evoked synchrony in regulating the compression of the visual code and suggest that distinct functions may be supported by different patterns of activity in the local circuit. However, data are lacking on how information coming from the upper cortical layers, where gamma synchrony occurs, is integrated by recipient neurons within and across cortical areas. A key follow-up to the results of Veit et al. may be to examine how visually evoked synchrony in the gamma band shapes information transfer from the upper cortical layers to downstream circuits.

Another key question is whether the extensive synaptic connections between the different classes of cortical inhibitory interneurons play a role in regulating the suppression of synchrony via VIP-SST interactions. The computational model presented by Veit et al. illustrates how VIP interneurons might regulate synchrony by inhibiting SST cells. However, for the sake of clarity, the impact of other I-I connections in the local circuit was not included in this current effort. VIP interneurons also receive robust inhi-

bition from SST cells. This strong reciprocal connection may play an important role in tipping the balance between synchronized and desynchronized regimes in the awake cortex. Likewise, other connections among inhibitory cell types may further refine the context-dependent recruitment of synchrony.

Finally, it is intriguing to ask whether the role of VIP interneurons in the regulation of synchrony generalizes to other regions of the cortex. Many cortical areas share a common layout where the connectivity of SST and VIP neurons is conserved,⁷ and the modeling work presented by Veit et al. illustrates how synchrony may naturally arise within this circuit. However, the circuit-level details of robust synchrony outside the primary visual cortex remain less well explored, and the degree to which the VIP-SST interaction is required for context-dependent regulation of local and long-range synchrony in other cortical areas is unknown. It would thus be interesting to test whether similar regimes of synchrony occur across sensory and associative cortical areas. Veit et al. pave the way to address these questions and open promising avenues for future comparative work.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Veit, J., Handy, G., Mossing, D.P., Doiron, B., and Adesnik, H. (2023). Cortical VIP neurons locally control the gain but globally control the coherence of gamma band rhythms. *Neuron* 111, 389–401. <https://doi.org/10.1016/j.neuron.2022.10.036>.
2. Buzsáki, G., and Wang, X.-J. (2012). Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* 35, 203–225. <https://doi.org/10.1146/annurev-neuro-062111-150444>.
3. Gray, C.M., König, P., Engel, A.K., and Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* 338, 334–337. <https://doi.org/10.1038/338334a0>.
4. Vinck, M., and Bosman, C.A. (2016). More Gamma More Predictions: Gamma-Synchronization as a Key Mechanism for Efficient Integration of Classical Receptive Field Inputs with Surround Predictions. *Front. Syst. Neurosci.* 10, 35. <https://doi.org/10.3389/fnsys.2016.00035>.
5. Veit, J., Hakim, R., Jädi, M.P., Sejnowski, T.J., and Adesnik, H. (2017). Cortical gamma band synchronization through somatostatin interneurons. *Nat. Neurosci.* 20, 951–959. <https://doi.org/10.1038/nn.4562>.
6. Chen, G., Zhang, Y., Li, X., Zhao, X., Ye, Q., Lin, Y., Tao, H.W., Rasch, M.J., and Zhang, X. (2017). Distinct Inhibitory Circuits Orchestrate Cortical beta and gamma Band Oscillations. *Neuron* 96, 1403–1418.e6. <https://doi.org/10.1016/j.neuron.2017.11.033>.
7. Tremblay, R., Lee, S., and Rudy, B. (2016). GABAergic interneurons in the neocortex: From cellular properties to circuits. *Neuron* 91, 260–292. <https://doi.org/10.1016/j.neuron.2016.06.033>.
8. Millman, D.J., Ocker, G.K., Caldejon, S., Kato, I., Larkin, J.D., Lee, E.K., Luviano, J., Nayan, C., Nguyen, T.V., North, K., Seid, S., White, C., Lecoq, J., Reid, C., Buice, M.A., and de Vries, S.E. (2020). VIP interneurons in mouse primary visual cortex selectively enhance responses to weak but specific stimuli. *Elife* 9, e55130. <https://doi.org/10.7554/elifesciences.55130>.
9. Ulan, C., Peter, A., Lazar, A., Barnes, W., Klon-Lipok, J., Shapcott, K.A., Roese, R., Fries, P., Singer, W., and Vinck, M. (2022). Predictive coding of natural images by V1 firing rates and rhythmic synchronization V1 firing rates and rhythmic synchronization. *Neuron* 110, 1240–1257.e8. <https://doi.org/10.1016/j.neuron.2022.01.002>.
10. Perrenoud, Q., Fonseca, A.H., de, O., Airhart, A., Bonanno, J., Mao, R., et al. (2022). Flexible perceptual encoding by discrete gamma events. *bioRxiv*. <https://doi.org/10.1101/2022.05.13.491832>.

Uncovering the rhythm for the expression of empathetic fear

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In this issue of *Neuron*, Kim et al.¹ demonstrate that theta oscillations between the right ACC and BLA are critical for observational fear and identify a role for the hippocampus in modulating these oscillations. They further show that theta oscillations are specifically involved in vicarious rather than directly experienced fear.

Key animal experiments have enhanced our understanding of fear conditioning. Classical conditioning is a form of learning in which one associates a neutral stimulus, known as a conditioned stimulus (CS), with a stimulus that naturally elicits a response, known as an unconditioned stimulus (US). When the two stimuli are repeatedly paired, the CS becomes capable of eliciting the same response as the US on its own, known as a conditioned response (CR). In rodents, an aversive form of conditioning is often carried out using a foot shock as a US given in a specific spatial context (the CS). Foot shocks elicit a robust conditioned fear response manifested as epochs of freezing behavior. By learning to associate foot shocks with the context, the

subjects will exhibit freezing epochs (the CR) whenever placed in the same context (the CS). In observational fear learning, the subject (observer) observes another animal (demonstrator) receiving foot shocks. In this paradigm, the US is the demonstrator's distress from receiving foot shocks, which naturally elicits freezing in the observer both during and after conditioning when placed in the same context.² In this observational learning, fear can be socially transmitted through vicarious observation without the observer directly experiencing the aversive stimulus.

Two main brain regions involved in this process have been identified—the anterior cingulate cortex (ACC) and the basolateral amygdala (BLA)—but the

mechanisms behind how these regions coordinate observational fear were uncharacterized.^{3–6} The BLA receives excitatory inputs from both the ipsilateral and contralateral ACC. It was previously demonstrated that the ACC in the right hemisphere explicitly plays a role in controlling observational fear.⁴ In the current study, Kim et al.¹ used optogenetic tools to specifically inhibit ACC inputs to the BLA from the right or the left hemisphere to show that inhibition of the right ACC projections to BLA impaired the observational fear response, as indicated by reduced freezing in the observer during conditioning. In contrast, inhibition of the left ACC projections to the BLA did not affect the expression of fear. The BLA reciprocally projects back to the ACC

