

unclear. The evidence supporting a defect in vesicle priming in CSP $\alpha$  KO mice is indirect. Direct evidence showing a decrease in the docked vesicle number, the readily releasable vesicle pool size, and/or the rate of vesicle mobilization to the readily releasable pool awaits further study. It also remains untested whether the defects in dynamin 1 polymerization and vesicle recycling cause synapse loss. This possibility has been challenged by a recent study showing that SNAP-25 overexpression is sufficient to rescue synapse loss and degeneration in cultured neurons derived from CSP $\alpha$  KO mice (Sharma et al., 2011a). In addition to SNAP-25 and dynamin 1, there are around 20 other proteins that are reduced in CSP $\alpha$  KO mice (Zhang et al., 2012). Further investigation is needed to understand how these other proteins are regulated by CSP $\alpha$  and whether their decrease contributes to synaptic dysfunction and loss observed in CSP $\alpha$  KO mice. The studies by Rozas et al. (2012) and Zhang

et al. (2012) have laid a foundation for future studies that will aim to resolve aforementioned questions.

#### REFERENCES

- Chandra, S., Gallardo, G., Fernández-Chacón, R., Schlüter, O.M., and Südhof, T.C. (2005). *Cell* 123, 383–396.
- Ferguson, S.M., Brasnjo, G., Hayashi, M., Wölfel, M., Collesi, C., Giovedi, S., Raimondi, A., Gong, L.W., Ariel, P., Paradise, S., et al. (2007). *Science* 316, 570–574.
- Fernández-Chacón, R., Wölfel, M., Nishimune, H., Tabares, L., Schmitz, F., Castellano-Muñoz, M., Rosenmund, C., Montesinos, M.L., Sanes, J.R., Schneggenburger, R., and Südhof, T.C. (2004). *Neuron* 42, 237–251.
- Hosoi, N., Holt, M., and Sakaba, T. (2009). *Neuron* 63, 216–229.
- Lin, Y.C., and Koleske, A.J. (2010). *Annu. Rev. Neurosci.* 33, 349–378.
- Nosková, L., Stránecký, V., Hartmannová, H., Přistoupilová, A., Barešová, V., Ivánek, R., Hůlková, H., Jahnová, H., van der Zee, J., Staropoli, J.F., et al. (2011). *Am. J. Hum. Genet.* 89, 241–252.

Rozas, J.L., Gómez-Sánchez, L., Mircheski, J., Linares-Clemente, P., Nieto-González, J.L., Vázquez, M.E., Luján, R., and Fernández-Chancón, R. (2012). *Neuron* 74, this issue, 151–165.

Schmid, S.L., and Frolov, V.A. (2011). *Annu. Rev. Cell Dev. Biol.* 27, 79–105.

Sharma, M., Burré, J., Bronk, P., Zhang, Y., Xu, W., and Südhof, T.C. (2011a). *EMBO J.* 31, 829–841.

Sharma, M., Burré, J., and Südhof, T.C. (2011b). *Nat. Cell Biol.* 13, 30–39.

Südhof, T.C., and Rizo, J. (2011). *Cold Spring Harb. Perspect. Biol.*, in press. Published online October 25, 2011. 10.1101/cshperspect.a005637.

Washbourne, P., Thompson, P.M., Carta, M., Costa, E.T., Mathews, J.R., Lopez-Bendito, G., Molnár, Z., Becher, M.W., Valenzuela, C.F., Partridge, L.D., and Wilson, M.C. (2002). *Nat. Neurosci.* 5, 19–26.

Wu, L.G., Ryan, T.A., and Lagnado, L. (2007). *J. Neurosci.* 27, 11793–11802.

Wu, X.S., McNeil, B.D., Xu, J., Fan, J., Xue, L., Melicoff, E., Adachi, R., Bai, L., and Wu, L.G. (2009). *Nat. Neurosci.* 12, 1003–1010.

Zhang, Y.-Q., Henderson, M.X., Colangelo, C.M., Ginsberg, S.D., Bruce, C., Wu, T., and Chandra, S.S. (2012). *Neuron* 74, this issue, 136–150.

## Familiarity Breeds Plasticity: Distinct Effects of Experience on Putative Excitatory and Inhibitory Neurons in Inferior Temporal Cortex

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Primates have a remarkable capacity to recognize a vast array of visual objects, an ability that depends on experience. In this issue of *Neuron*, Woloszyn and Sheinberg (2012) report that putative excitatory and inhibitory neurons in inferior temporal cortex exhibit distinct influences long-term visual experience.

Humans and other primates have an astonishing ability to recognize many thousands of unique visual objects, from faces and food items to natural and man-made objects. We are not born with a large innate library of familiar objects that we are able to recognize. Instead, our recognition ability depends on learning and experience. Experience

can also produce a significant improvement in visual discrimination. For example, an expert bird watcher might easily distinguish between two individuals from the same species, while a less experienced observer might be unable to distinguish them. In addition to identification and discrimination, humans and other animals are sensitive to whether

a stimulus is familiar (Fagot and Cook, 2006), sometimes even for stimuli that had been viewed infrequently in the past and about which no other details can be recalled.

Neurophysiological investigations of object recognition have focused on a hierarchy of cortical areas including area V4 and the posterior and anterior



connections between cortical areas originate predominantly from excitatory pyramidal neurons; thus, the stronger and sharper representations of familiar stimuli would support more efficient read-out of object identity from excitatory ITC neurons.

These results help to reconcile the conflicting findings from earlier studies. As the authors point out, previous studies which reported stronger responses to familiar stimuli tended to use large and diverse stimulus sets and/or screened neurons to identify their preferred stimuli. Thus, these studies were more likely to test neurons with preferred stimuli that would drive strong responses. Studies which found either weaker or equivalent firing rates for familiar compared to novel stimuli often used smaller stimulus sets, chose stimuli from a relatively restricted region of object space, or made no efforts to identify neurons' preferred stimuli. Furthermore, all prior studies almost certainly sampled both excitatory and inhibitory neurons, but did not analyze those populations separately. The authors point out that when both classes of neurons are combined in population analyses, the increased response of the excitatory population to preferred familiar stimuli would be at least partially counterbalanced by the opposite effect in the inhibitory population. Along with the differences in the stimuli and experimental procedures, this may account much of the variability across previous studies.

This study lends support to the idea that object recognition is mediated by a sparse code in ITC, in which objects are each represented by small populations of exquisitely tuned neurons. The current study suggests that learning would facilitate this coding scheme by increasing the response rate and sharpness of selectivity for neurons' preferred familiar stimuli. As described above, this could lead to improvements in the ability of downstream areas to read out object information from excitatory projection neurons in ITC. Important questions remain regarding the encoding of object representations in ITC. For example, studies which did not optimize stimuli or used small or homogeneous stimulus sets typically find highly significant stimulus selectivity for the tested stimuli

despite weaker firing rates (Baker et al., 2002; Sigala and Logothetis, 2002; Freedman et al., 2006). Thus, in addition to responding very strongly to an optimal stimulus, ITC neurons also have the ability to discriminate between their nonpreferred stimuli. However, the degree to which object recognition is mediated by the few neurons that are optimally tuned for a stimulus or, instead, by the larger and more distributed population that is responding selectively (but at nonoptimal rates) remains to be determined.

A number of related questions remain to be examined in future work. For example, the current study examined ITC activity during a passive viewing task with limited behavioral demands. Thus, it will be interesting to compare the patterns of selectivity in putative excitatory and inhibitory neurons during more active and demanding tasks such as discrimination or memory-based matching. One way to assess whether recognition relies predominantly on the subset of strongly responsive excitatory neurons is to ask whether the activity of those neurons is better correlated with animals' trial-by-trial perceptual judgments than other neuronal populations. A second question to explore is how ITC object representations change during the learning process itself. In the current study, monkeys were familiarized with a set of stimuli for several months prior to ITC recordings. Additional work is needed to characterize the time course of experience-dependent changes in ITC, and to explore whether putative excitatory and inhibitory neurons play distinct roles during the learning process as they appear to do once learning is complete.

An intriguing effect observed in both this study and previous work is that experience results in a marked decrease in average activity across the ITC population (Li et al., 1993; Fahy et al., 1993; Freedman et al., 2006)—except for the (presumably few) excitatory neurons that happen to be well tuned to the currently-viewed stimulus. As noted above, humans and other animals are highly sensitive to whether a stimulus is familiar or novel. An interesting issue for future work will be to examine the relationship between neuronal familiarity effects in ITC and

behavioral effects of novelty and familiarity. One hypothesis is that the widespread experience-dependent suppression of activity in ITC underlies our ability to detect novelty and familiarity. Further, it will be interesting to examine how novelty and familiarity signals in ITC relate to attention, as novel or unexpected stimuli are often highly effective for capturing attention.

In summary, the results of this study are an important contribution to our understanding of the neural circuitry underlying visual object recognition and, in particular, how experience influences shape selectivity in ITC. More broadly, the observation that different cell classes show distinct effects of learning points out the need for new tools, analytical approaches, and *in vivo* data acquisition techniques for recording neuronal activity along with anatomical and morphological information about the recorded neurons (e.g., neuron type, cortical layer, and pattern of connections). This will ultimately be essential for developing a detailed circuit-level understanding of the neural basis of visual recognition.

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#### REFERENCES

- Baker, C.I., Behrmann, M., and Olson, C.R. (2002). *Nat. Neurosci.* 5, 1210–1216.
- Connor, C.E., Pasupathy, A., Brincat, S., and Yamane, Y. (2009). In *The Cognitive Neurosciences IV, Fourth Edition*, M.S. Gazzaniga, ed. (Cambridge, MA: MIT Press).
- Diester, I., and Nieder, A. (2008). *J. Neurosci.* 28, 7737–7747.
- Fagot, J., and Cook, R.G. (2006). *Proc. Natl. Acad. Sci. USA* 103, 17564–17567.
- Fahy, F.L., Riches, I.P., and Brown, M.W. (1993). *Exp. Brain Res.* 96, 457–472.
- Freedman, D.J., Riesenhuber, M., Poggio, T., and Miller, E.K. (2006). *Cereb. Cortex* 16, 1631–1644.
- Hussar, C.R., and Pasternak, T. (2009). *Neuron* 64, 730–743.
- Kobatake, E., Wang, G., and Tanaka, K. (1998). *J. Neurophysiol.* 80, 324–330.
- Li, L., Miller, E.K., and Desimone, R. (1993). *J. Neurophysiol.* 69, 1918–1929.

Logothetis, N.K., Pauls, J., and Poggio, T. (1995). *Curr. Biol.* 5, 552–563.

McCormick, D.A., Connors, B.W., Lighthall, J.W., and Prince, D.A. (1985). *J. Neurophysiol.* 54, 782–806.

Mitchell, J.F., Sundberg, K.A., and Reynolds, J.H. (2007). *Neuron* 55, 131–141.

Moeller, S., Freiwald, W.A., and Tsao, D.Y. (2008). *Science* 320, 1355–1359.

Sigala, N., and Logothetis, N.K. (2002). *Nature* 415, 318–320.

Woloszyn, L., and Sheinberg, D.L. (2012). *Neuron* 74, this issue, 193–205.