the type of cultures they used. An earlier electrophysiological study found that the depletion of releasable vesicles occurred more readily in inhibitory synapses from synapsin I null mice[11].

Real-time visualization of synapsins and other proteins, as developed by Chi and colleagues[2], adds a powerful analytical method to the existing array of techniques used to study presynaptic function. It permits analysis of the dynamics of presynaptic molecules *in situ* while monitoring synaptic function. Imaging biochemistry inside living synapses in real time will no doubt facilitate analysis of mechanisms in vesicle trafficking.

1. Greengard, P., Valtorta, F., Czernik, A. J. & Benfenati, F. *Science* **259**, 780–785 (1993).
2. Chi, P., Greengard, P. & Ryan, T. A. *Nat. Neurosci.* **4**, 1187–1193 (2001).
3. Li, L. *et al. Proc. Natl. Acad. Sci. USA* **92**, 9235–9239 (1995).
4. Rosahl, T. W. *et al. Nature* **375**, 488–493 (1995).
5. Hilfiker, S. *et al. Nat. Neurosci*, **1**, 29–35 (1998).
6. Humeau, Y. *et al. Neuroscience* **21**, 4195–4206 (2001).
7. Sihra, T. S., Wang, T. K., Gorelick, F. S. & Greengard, P. *Proc. Natl. Acad. Sci. USA* **86**, 8108–8112 (1989).
8. Torri-Tarelli, F., Bossi, M., Fesce, R., Greengard, P. & Valtorta, F. *Neuron* **9**, 1143–1153 (1992).
9. Hosaka, M., Hammer, R. E. & Sudhof, T. C. *Neuron* **24**, 377–387 (1999).
10. Li, Z. & Murthy, V. N. *Neuron* **31**, 593–605 (2001).
11. Terada, S., Tsujimoto, T., Takei, Y., Takahashi, T. & Hirokawa, N. J. *Cell Biol.* **145**, 1039–1048 (1999).

Synaptic connectivity and computation

Anthony M. Zador

A new study finds two classes of synapses between layer 2/3 neurons in auditory cortex, and suggests they may be involved in processing transient versus sustained acoustic stimuli

What endows a cortical circuit with its unique identity? How does a bit of cortex implement the computation that it must perform? The simple answer, of course, is that function arises from the pattern of synaptic connection between neurons and the strengths of these connections. This view motivates much research on synaptic function and plasticity, and is enshrined in formal neural network models of computation. There is, however, remarkably little experimental evidence detailing how a particular matrix of synaptic connectivity gives rise to a particular computation.

Atzori and colleagues[1] advance an intriguing hypothesis that begins to bridge this gap between cortical computation and synaptic mechanism. Using dual whole-cell patch-clamp recordings, they examined the properties of synaptic connections between pairs of coupled neurons in layer 2/3 of acute slices of auditory cortex. In the rat, these layer 2/3 neurons (along with neurons in layer 4) receive direct input from the auditory thalamus; layer 2/3 neurons in turn make connections both to other layer 2/3 neurons, and to layer 5 neurons. Atzori *et al.* found that these layer 2/3 connections fell into two classes, 'weak' and 'strong,' which differed in a number of important characteristics, including average amplitude, failure rate and paired pulse ratio. Most notably, these connections differed in their temporal dynamics, as assessed by the response to a sustained train of action potentials. Strong connections decayed during the train, while weak connections retained their efficacy at a constant, albeit lower, level throughout the train. Strong connections thus gave their most robust responses to the transient portion of stimuli, while weak connections responded equally well to both transient and sustained stimuli. By contrast, synaptic characteristics between pairs of layer 2/3 neurons in the barrel cortex fell into a third category, which might be called 'very strong.'

The authors noted an interesting parallel between these two synaptic classes identified in auditory cortex and the two types of firing patterns—'transient' and 'sustained'—with which thalamic inputs to the auditory cortex respond to acoustic stimuli. They suggest that the two classes of synaptic connection might provide two distinct, parallel channels within the cortex for processing information about these two kinds of auditory stimuli, just as the magnocellular and parvocellular pathways provide separate pathways in the visual system for processing different kinds of visual stimuli.

The core of the present findings relates to the physiological properties underlying excitatory coupling between neuronal pairs of layer 2/3 of the cortex. According to the classical quantal model[2], synaptic transmission is a probabilistic process in which the presynaptic terminal is coupled to its postsynaptic target through a set of n release sites. When an action potential invades the presynaptic terminal, each of the sites releases a vesicle of neurotransmitter with a probability p (and therefore fails to release with probability $1 - p$); the postsynaptic response due to the vesicle is given by the quantal size q (which has units of mV or pA). The total postsynaptic response R following an action potential is thus given by the simple equation:

$$R = n\,p\,q \qquad (1)$$

Together, the product of the three quantal variables n, p and q governs the average synaptic response R, with weak synapses having a smaller product than strong synapses.

Although the quantal model was originally developed to describe events at the neuromuscular junction, the same framework, with relatively minor modifications, has been able to account for transmission at central synapses as well. One important difference is quantitative. At the neuromuscular junction, the number of release sites is typically

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quite large ($n \sim 10^4$), whereas the number of release sites mediating the coupling between a pair of neurons in the cortex (including both neocortex and hippocampus) is much smaller, often near one. The smaller value at central synapses has made it easier to study not just the aggregate statistical properties of release sites, as at the neuromuscular junction, but differences among them as well.

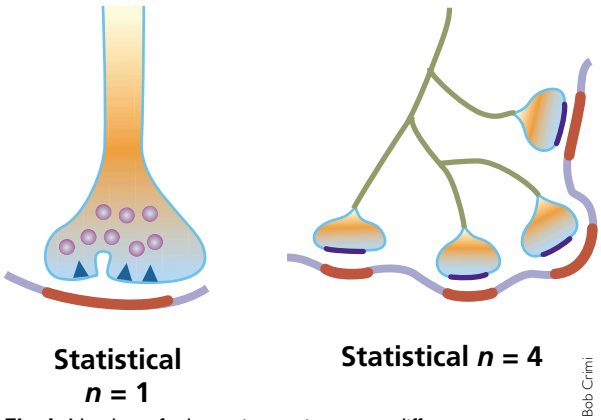

Fig. 1. Number of release sites varies among different synapses.

Strong and weak connections differ in their release probability. Part of this difference may be due to differences in the number of release sites, n, between those two connections (**Fig. 1**); even small differences in the number of release sites among synaptic populations can alter the interpretation of experimental results. In the hippocampus, the well-studied Schaffer collateral connection between neurons in regions CA3 and CA1 is usually mediated by only a single release site[3], whereas in the neocortex a single axon from one neuron may make several contacts—as many as a dozen—onto its target[4]. A complete failure of synaptic transmission following an action potential is an exponentially rare event when the synaptic coupling between two neurons involves multiple release sites: for n release sites, each with a probability p of release and $1 - p$ of failure, the probability that all n sites will fail simultaneously is given by $(1 - p)^n$, a quantity that diminishes rapidly with increasing n. Thus the difference in the failure rate between weak, strong and very strong synapses may arise in part through differences in the number of release sites n, rather than through differences in the release sites themselves.

Strong and weak connections may differ not only in the number of release sites n, but also in the release probability p at each release site. Recent studies of central synapses have revealed remarkable heterogeneity among release sites. Heterogeneity of release probability has been demonstrated by a wide range of experimental techniques, including minimal stimulation[5], paired neuronal recording[6], and optical[7] and pharmacological[8,9] methods. Even synapses within an ostensibly homogeneous population, such as those arising from a single presynaptic axon and terminating on a single postsynaptic target (as in autaptic cultures), have different release probabilities[7,8].

Central synapses differ in their temporal dynamics as well. Synaptic efficacy during a train of action potentials can increase or decrease, depending on the properties of the synapse and the temporal dynamics of the input spike train. The complexity of these synaptic dynamics arises from the interplay of a host of physiologically distinct mechanisms, including paired pulse facilitation, paired pulse depression and post-tetanic potentiation, operating on characteristic time scales ranging from milliseconds to seconds or more[10]. Most forms of short-term plasticity are mediated by changes in release probability. Indeed, there is an inverse relation between the initial synaptic release probability and the amount of short-term facilitation at single release sites (that is, sites with high release probability depress[5]). This is consistent with the tendency of strong, high probability connections in layer 2/3 of auditory cortex to show depression in response to sustained stimulation[1].

Heterogeneity in the temporal dynamics of synaptic responses provides a rich substrate for cortical circuits to implement different computations. Synaptic dynamics are themselves subject to plasticity. Changes in temporal processing in the auditory cortex have been observed following perturbations of sensory experience[11], but the cellular and synaptic mechanisms underlying these changes have not been examined. In the somatosensory (whisker) system of the rat, sensory deprivation leads to a reorganization of the pattern of cortical responsiveness, and to corresponding changes in the average characteristics of synaptic dynamics in both vertical and horizontal excitatory pathways[12]. These changes might be due to changes in the temporal dynamics of individual synapses, or to a change in the relative contribution of populations with different characteristic dynamics[13]. The possibilities for temporal processing offered by dynamic synapses are only beginning to be explored in the context of formal neural network models[14].

Atzori and colleagues[1] have proposed a thought-provoking and testable hypothesis—that the two classes of synaptic connection between layer 2/3 neurons in auditory cortex provide a substrate for differential processing of transient versus sustained acoustic stimuli. It should be emphasized that, by virtue of the preparation they used (*in vitro* recording in acute slices), their experimental results provide no direct support for this idea, not even correlative. Testing this hypothesis will require an experimental approach that can link synaptic and sensory physiology. The potential payoff for such challenging experiments is the opportunity to understand how networks of cortical neurons implement their computations.

1. Atzori, M. *et al. Nat. Neurosci.* **4**, 1230–1237 (2001).
2. del Castillo, J. & Katz, B. *J. Physiol. (Lond.)* **124**, 560–573 (1954).
3. Sorra, K. E. & Harris, K. M. *J. Neurosci.* **13**, 3736–3748 (1993).
4. Markram, H. *Cereb. Cortex* **7**, 523–533 (1997).
5. Dobrunz, L. E. & Stevens, C. F. *Neuron* **18**, 995–1008 (1997).
6. Markram, H., Wang, Y. & Tsodyks, M. *Proc. Natl. Acad. Sci. USA* **95**, 5323–5328 (1998).
7. Murthy, V. N., Sejnowski, T. J. & Stevens, C. F. *Neuron* **18**, 599–612 (1997).
8. Rosenmund, C., Clements, J. D. & Westbrook, G. L. *Science* **262**, 754–757 (1993).
9. Hessler, N. A., Shirke, A. M. & Malinow, R. *Nature* **366**, 569–572 (1993).
10. Koch, C. *Biophysics of Computation* (Oxford Univ. Press, New York, 1999).
11. Kilgard, M. P. & Merzenich, M. M. *Nat. Neurosci.* **1**, 727–731 (1998).
12. Finnerty, G. T., Roberts, L. S. & Connors, B. W. *Nature* **400**, 367–371 (1999).
13. Poncer, J. C. & Malinow, R. *Nat. Neurosci.* **4**, 989–996 (2001).
14. Natschlager, T., Maass, W. & Zador, A. M. *Network* **12**, 75–87 (2001).