neurological disorders featuring cognitive deficits, development of more selective Arc inhibitors has exciting therapeutic potential. Given the large and growing list of Arc binding partners, the effects of inhibiting Arc could be variable and difficult to predict. Assessing efficacy in Angelman syndrome models would be, perhaps, the most reasonable starting point, as increased levels of Arc are directly implicated in its etiology.

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Balancing Excitation and Inhibition

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In this issue of *Neuron*, D'amour and Froemke (2015) examine how inhibitory spike-time-dependent plasticity (STDP) interacts with co-activated excitatory STDP to regulate excitatory-inhibitory balance in auditory cortex.

Cortical processing depends on glutamatergic excitatory synapses to propagate neural firing and on GABAergic inhibitory synapses to shape the temporal and spatial patterns of firing. In an active cortex, changes in excitatory synaptic drive are often matched by corresponding changes in inhibitory synaptic drive, supporting the notion that cortical processing depends critically on the balanced interplay of excitation and inhibition (E/I balance) (Isaacson and Scanziani, 2011), a balance that is dynamically maintained (Tao et al., 2014; Xue et al., 2014; Zhou et al., 2014). Indeed, alterations in the E/I balance impair essential features of the cellular response in sensory cortices, including dynamic range, stimulus selectivity, and gain control (Isaacson and Scanziani, 2011), and also impair learned performance in prefrontal cortex (Yizhar et al., 2011). E/I alterations have also been implicated in autism and schizophrenia. On the other hand, cortical circuits not only process information, but also store it as changes in the strength of glutamatergic connectivity, and this plasticity allows adaptive responses to altered sensory experience. Notably, in the cases examined, in the long run experience-dependent remodeling of the excitatory connectivity is accompanied by changes in inhibitory circuits such that the E/I is maintained (Froemke et al., 2007; House et al., 2011). Thus, adaptive cortical plasticity, for example, lowering the threshold for a particular sensory stimulus, might not compromise the conditions for processing other stimuli. At a synaptic level, these observations also raise the important question of whether mechanisms that allow plasticity of excitatory and inhibitory synapses can be coordinated. The answer is yes, as documented by the D'amour and Froemke analysis of spike-timing-dependent plasticity (STDP) in the auditory cortex reported in this issue of *Neuron* (D'amour and Froemke, 2015).

STDP is an attractive model of synaptic plasticity as it is induced by near-coincidental (within tens of milliseconds) pre- and postsynaptic activation. In most glutamatergic cortical synapses STDP tends to follow the Hebbian rule resulting in long-term potentiation (LTP) or depression (LTD) depending on whether the

pre- or the postsynaptic element fires first. A theoretical study, on the other hand, showed that a stable E/I balance could be easily achieved if different STDP rules govern the modification of GABAergic synapses (Vogels et al., 2011). Specifically, it requires that LTP occurs whenever pre- and postsynaptic firing coincide, but independently of the firing order, and that LTD occurs whenever the presynaptic element fires alone. This combination of Hebbian and non-Hebbian rules for excitatory and inhibitory synapses would provide a self-correcting mechanism that over multiple iterations would converge onto a set E/I balance. D'amour and Froemke (2015) examined the rules for inducing STDP simultaneously in subsets of excitatory and inhibitory inputs contacting a given pyramidal cell of the auditory cortex, and evaluated their impact on the E/I balance. They did the experiments in slices and used extracellular stimulation to evoke a compound of glutamatergic and GABAergic synaptic responses in the same cell. To distinguish these two components, they used the trick of recording under voltage clamp at two different voltages corresponding to their respective reversal potentials (close to the resting potential for excitatory currents, closer to zero for inhibitory currents), and used the ratio of these current values as an index of the E/I balance. To induce STDP, they switched to current clamp (to allow postsynaptic firing), and then switched back again to voltage clamp to evaluate the changes in excitatory and inhibitory responses.

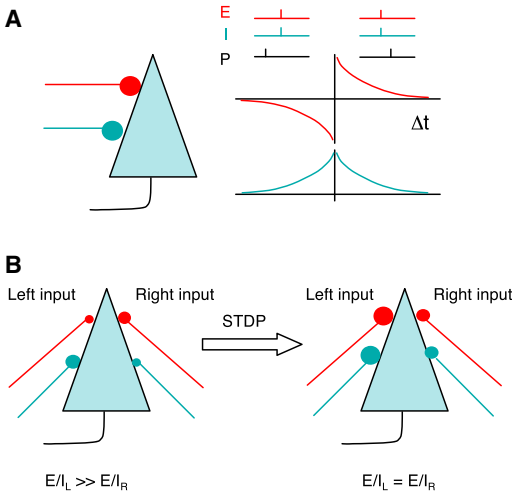

Figure 1. STDP in Co-activated Excitatory and Inhibitory Synapses

(A) Distinct STDP rules apply for co-activated excitatory synapses (red) and inhibitory synapses (green) contacting a pyramidal cell (gray).

(B) LTP on inhibitory synapses is related to the initial E/I ratio. As a result, after STDP the E/I ratios for different inputs tend to converge.

The results confirmed some of the expectations. Not surprisingly, STDP of the glutamatergic component was Hebbian with LTP induced when presynaptic firing preceded postsynaptic firing, and LTD induced with the opposite order of firing. STDP of the inhibitory component was non-Hebbian, with LTP induced independently of the order of pre- and postsynaptic firing, which is in partial agreement with the anticipated theoretical rule (illustrated in Figure 1A). An interesting consequence of this outcome is that STDP allows for an increase in the precision of neural firing. In cortical circuits, feedforward and feedback inhibition is always delayed in relation to excitation, defining a time window for postsynaptic action potential firing (before inhibition fully develops). After conditioning with pre- and postsynaptic stimulation, the strengthening (LTP) of excitation increases the probability of firing action potentials, while the strengthening of inhibition shortens the temporal window for firing action potentials. On the other hand, after conditioning with the opposite pairing (postsynaptic then presynaptic) the probability of firing action potentials is reduced not only by the depression of synaptic excitation, but also by the strengthening of synaptic inhibition. Thus, one consequence of having distinct STDP rules for excitation and inhibition is to increase the contrast between potentiated and depressed inputs.

Other expectations were not confirmed. The theoretical study mentioned above posed that a stable E/I balance will result if LTP of inhibition follows near-coincidental pre- and postsynaptic firing, while presynaptic firing alone produces inhibitory LTD (Vogels et al., 2011). No overt evidence for such LTD rule was found, however. How could an E/I balance be achieved then? D'amour and Froemke (2015) observed that the magnitude of inhibitory LTP did relate to the value of the initial E/I ratio: the larger the E/I ratio, the larger the inhibitory LTP. As a consequence, despite an initial variability, after STDP the E/I ratio tended to converge to a common value (illustrated in Figure 1B). A surprisingly simple, yet effective rule solves the problem of restoring the E/I balance and opens a set of interesting questions, too. First, it remains to be determined how universal the mechanism is: does it work in other pyramidal cells? Also, how is inhibitory strength eventually reduced? Inhibitory STDP is unidirectional: it only potentiates. How is saturation of inhibition prevented? But perhaps the most interesting questions concern the mechanisms. How does the cell sense the E/I balance, how does it compute the difference between the actual and the targeted E/I balance, and how does it produce a signal to adjust the inhibitory strength accordingly?

Cortical excitation and inhibition are likely balanced by the interactions of multiple mechanisms operating at different temporal and spatial scales. At the circuit level, for example, changes in the recruitment of feedforward and feedback inhibition profoundly impact the E/I balance evoked by sensory stimulation (Gu et al., 2013; Kuhlman et al., 2013). That recruitment, in turn, depends on the strength of highly plastic excitatory inputs onto interneurons (House et al., 2011; Huang et al., 2013). The demonstration of a mechanism that regulates the E/I balance in a cell-autonomous manner is an important step toward a comprehensive understanding of the E/I balance.

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Making Decisions Based on Autobiographical Memories

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A new human intracranial study by Foster et al. (2015) sheds light on the electrophysiological correlates of intrinsic and task-evoked functional connectivity in lateral and medial parietal cortex.

Remembering events from our past (e.g., a movie we watched or what we had for lunch yesterday) is a perfunctory task that we do countless times each day, and yet its neural underpinnings remain poorly understood. These processes have remained difficult to study because they involve directing attention to and making decisions based on internal states. In contrast, the mechanisms of making decisions based on sensory inputs is better understood, but it is still largely unknown if these mechanisms are also engaged for decisions based on internal signals.

Episodic memory retrieval is an internally directed process that can be initiated by external cues, making it amenable to systematic study. In addition to the medial temporal lobes, a number of other cortical and subcortical areas are essential to encode and retrieve episodic memories. Chiefly among those are areas of the posterior parietal cortex (PPC), including the posterior cingulate cortex (PCC), angular gyrus (AG), and retrosplenial cortex (RSC). These areas are activated by episodic memory retrieval tasks as assessed by hemodynamic activity (Wagner et al., 2005).

The default mode network (DMN) encompasses many areas, including parts of the PPC, which are active during rest and/or internally focused tasks such as memory retrieval and other self-referential activities (Buckner et al., 2008). In contrast, areas in the DMN are de-activated in tasks requiring goal-directed attention and working memory. The DMN is one of a number of such large-scale networks that have been proposed based on brain imaging studies. Other networks that have been explored in task-related and resting state conditions include the dorsal attentional network, the executive working memory network, the primary motor network, and the primary visual network (Toro et al., 2008). Collectively, this body of literature represents a shift from a modular interpretation of cognitive function to a paradigm that emphasizes distributed yet coordinated function across large-scale brain networks.

Much of the evidence on large-scale brain networks comes from non-invasive imaging studies that rely on indirect hemodynamic measures of brain activity. However, the functional significance of these networks remains poorly understood. Why are these areas more active during rest? Does their hemodynamic co-variation imply that individual neurons in these areas preferentially communicate with each other (Fries, 2005)?

In this issue, a new study by Foster et al. (2015) sheds light on these questions by directly recording neuronal activity from the lateral and medial parietal cortex of three human subjects as they performed simple memory tasks. Subjects were patients with epilepsy that were implanted with invasive subdural grid and strip electrodes to localize the onset of their seizures. The authors focus on two parietal areas: AG and RSC/PCC (Figure 1A). Hemodynamic activities in these two areas co-vary at rest, are part of the default-mode network, and are activated during episodic memory retrieval (Vann et al., 2009; Wagner et al., 2005). Subjects made true/false judgments in response to four types of statements: self-episodic (e.g., "I ate fruit yesterday"), self-semantic (e.g., "I eat fruit often"), self-judgment (e.g., "I am an honest person"), and other-judgment (e.g., "My neighbor is an