

to specify axonal trajectories and target specificity of individual motor neuron subtypes (Jessell, 2000; Shirasaki and Pfaff, 2002). Whether LIM homeodomain transcription factors act similarly to specify the architecture of limbic-hypothalamic circuitry needs to be confirmed, for this would imply that the “LIM codes” being defined for spinal motor neurons may generalize to forebrain circuitry.

In addition to the anatomical studies, the authors provide new insight into how these pathways may operate as “choice points” between incompatible behaviors. The pathway-specific projections of *Lhx6*-expressing neurons in the MEApd show preferential activation by reproductive olfactory cues such as female urine. In contrast, these cells appear unresponsive to a predator stimulus, cat odor, which was effective in activating neurons in the MEApv that do not respond to reproductive odors. Moreover, the *Lhx6* neurons in the MEApd appear to be inhibitory, while the neurons in MEApv that respond to cat odor are excitatory, based on expression of chemical markers for GABA and glutamate. The surprising finding that the MEApv also contains a subpopulation of these neurons that project to the VMHvl raises the possibility that the reproductive part of the VMH represents a point of convergence for limbic-hypothalamic pathways transmitting olfactory cues for reproduction and defensive behavior. The authors propose that because the projections from the MEApd are inhibitory, and those from the MEApv excitatory, they may exert opposing actions on GABAergic neurons in the VMHvl, thereby allowing activation of reproductive circuits and suppression of defensive behaviors when presented with a reproductive stimulus. However, upon presentation of a predator stimulus, excitation of GABAergic neurons in the VMHvl by glutamatergic neurons in the MEApv would interrupt reproductive behaviors in favor of defensive actions that promote individual survival. Thus, LIM homeodomain proteins may specify essential patterns of connectivity and neurotransmitter phenotypes that respond to behaviorally specific olfactory cues. Future work will determine if this circuitry allows animals to put love on hold and fight first, in order to live another day to reproduce.

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## Expecting the Unexpected: Modeling of Neuromodulation

An important aspect of decision-making is the need to make interpretations and predictions in the face of uncertain information. In this issue of *Neuron*, Yu and Dayan describe a model of the role of acetylcholine and norepinephrine in balancing top-down expectation and bottom-up sensory input in guiding behavior. The model builds from data on physiological effects of modulators regulating the balance of cortical feedback and thalamic input.

The study of neuromodulation needs computational modeling. The effects of neuromodulators are spatially diffuse and temporally slow, and computational models prove important for understanding how neuromodulators shift the functional state of neuronal populations. The article by Yu and Dayan in this issue of *Neuron* (Yu and Dayan, 2005) presents an exciting model that provides an important unifying framework for the role of the neuromodulators acetylcholine (ACh) and norepinephrine (NE) in behavioral confidence about sensory cues guiding choices.

In the model, ACh codes expected uncertainty about a specific cue (higher levels of ACh indicate a less reliable cue), whereas NE codes the unexpected uncertainty about the identity of a cue (if a cue proves unexpectedly unreliable, higher NE induces use of a different cue). The model is tested in a modified Posner attention task, in which central arrows provide cues for later appearance of a target stimulus on the left or right side, but the cues are not always reliable. If a cue is usually reliable, subjects guide responses based on the cue, leading to short reaction times for correct cues and long reaction times for incorrect cues. This difference in reaction times is called the validity effect. The model effectively simulates data (Witte et al., 1997; Phillips et al., 2000) showing how cholinergic drugs alter the valid-

ity effect. Blockade of muscarinic cholinergic receptors with scopolamine increases the validity effect, whereas activation of nicotinic cholinergic receptors reduces the validity effect.

As an analogy for this task, imagine two dogs named Ollie and Holly that bark when there is a visitor at the front or back door. Ollie reliably runs to the door with the visitor and barks there, whereas Holly barks more at either door. Because Ollie is reliable, if you hear him bark at the front door, you will walk there without waiting for a knock. You will reach the front door more rapidly, but if the visitor is at the back door, he or she must wait much longer. This difference in time is analogous to the validity effect. Scopolamine makes you rely on the bark and listen less for a knock, increasing the time difference if the dog barks at the wrong door. Nicotine enhances attention to the knock, reducing the validity effect similar to the unreliable bark of Holly.

This new model is based on physiological effects of ACh on synaptic transmission within cortical structures (Hasselmo and McGaughy, 2004), which influence reliance on cue memory as summarized in Figure 1. ACh reduces the effect of top-down cue expectation due to muscarinic presynaptic inhibition of excitatory glutamatergic feedback synapses from higher cortical areas (Hasselmo and Cekic, 1996). Simultaneously, ACh enhances the influence of afferent sensory input (the target) on cortical pyramidal cells, due to nicotinic receptors enhancing thalamocortical transmission (Gil et al., 1997) and muscarinic receptors depolarizing pyramidal cells (Hasselmo and McGaughy, 2004). Scopolamine blocks the cholinergic suppression of cortical feedback, thereby increasing top-down expectation and increasing the validity effect. Nicotine enhances the effect of thalamocortical sensory input, reducing reliance on top-down cue expectation and reducing the validity effect.

Cellular effects of NE are similar to ACh, including presynaptic inhibition of feedback synapses and of neuronal adaptation. However, behavioral data and recordings from the locus coeruleus (Aston-Jones et al., 1998) support a different functional role. In the model, NE levels increase when a threshold of expected uncertainty is passed, and norepinephrine shifts the network to use a different cue identity. Analogously, if your reliable dog Ollie started leading you to the wrong door consistently, you might decide something is wrong with him and try listening to Holly. This role of NE is consistent with behavioral data showing enhanced switching of task strategy with NE agonists, and perseverative behavior with reduced NE (Sara, 1998). The threshold of uncertainty is a particularly interesting finding of the model, as it explains evidence for competition between these modulators. Higher levels of ACh indicate higher expected uncertainty, requiring greater unexpected uncertainty to induce a switch (the unreliable dog Holly would have to make a larger number of errors before you would decide something was wrong with her). The modified Posner task used in the paper is experimentally intriguing, as it would allow simultaneous testing of both proposed modulatory functions.

A strength of this model is its ability to address modulatory effects in a range of tasks, including the role of

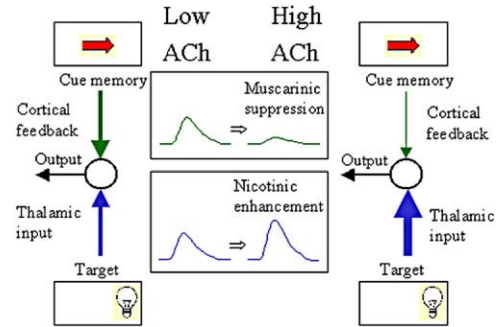


Figure 1. Modulatory Effects of Acetylcholine that May Influence Performance in the Posner Task

(Left) Low levels of acetylcholine (ACh) allow strong synaptic transmission at cortical feedback synapses, allowing a strong influence of top-down expectation based on the cue relative to sensory input from the target. (Right) High levels of ACh activate muscarinic receptors that cause presynaptic inhibition of cortical feedback. This reduces the influence of top-down expectation. ACh also activates nicotinic receptors that enhance thalamocortical input, thereby enhancing the influence of target input.

NE in extradimensional shifts of attentional set as shown by McGaughy, the role of ACh in stimulus detection tasks testing vigilance (Sarter et al., 2005), and the role of ACh in tasks testing the effect of previous stimulus reliability on new learning (Baxter et al., 1999). This type of modeling allows research to move beyond a spurious conflict between theories of attention versus memory and instead focus on linking behavioral function directly to underlying physiology. The model provides a useful and innovative step in applying Bayesian statistics to this field but raises many tough questions about the biological mechanisms for the processes it describes. As shown here, the role of ACh in balancing the effect of target versus cue can be mapped to cellular physiological data on modulation of synaptic transmission, but other mechanisms remain unclear, such as how an increase in NE will induce a shift in the expected cue identity. Though the model is abstract in its mechanistic elements, it makes clear predictions about behavioral phenomena and the time course of modulatory levels. This will prove useful to researchers who will benefit from this cohesive theoretical framework for evaluating neuromodulatory effects.

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