neous neuronal activity could allow the expression of multiple functional receptors in each ORN and underlie the aberrant axonal targeting and "wandering" that was previously associated with cells expressing additional ORs. In mice overexpressing Kir2.1 in mature ORNs, both P2 and MOR28 axons were diffusely distributed through the olfactory bulb and appeared to innervate multiple glomeruli. The tools are now in hand to directly examine the relationship between spontaneous activity and feedback regulation of OR selection.

In addition to the specific alterations arising from activity-dependent competition at individual glomeruli, Yu et al. report that there are global effects of eliminating spontaneous activity during development. The silencing of ORNs by hyperpolarization results in impaired axon extension. The most striking defects are seen in those axons that travel the greatest distance to the dorsal posterior olfactory bulb. In the visual system, electrical activity dramatically enhances trophic factor-mediated axon outgrowth in retinal ganglion cells (Goldberg et al., 2002). In a similar manner, neuronal activity may promote ORN responsiveness to guidance cues in the olfactory bulb.

Complex neuronal circuitry within the olfactory bulb is critical for enhancing the sensitivity and selectivity of olfactory perception. Recent studies have implicated a role for spontaneous spiking activity in shaping neuronal circuits. The refinement of the retinotopic map requires spontaneous retinal waves during development (McLaughlin et al., 2003). Olfactory neurons also exhibit a bursting behavior and a spontaneous firing of action potentials. A major future challenge lies in determining how intrinsic developmental processes, spontaneous activity from ORNs, and evoked activity arising from a dynamic odor environment contribute to olfactory bulb organization. Elucidating the mechanisms underlying the establishment of the olfactory sensory map and its interpretation by the CNS will be essential for understanding olfactory perception.

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Selective Dopamine Filter of Glutamate Striatal Afferents

Corticostriatal glutamate afferents and mesostriatal dopamine afferents commonly converge onto the same postsynaptic spines of medium projection neurons. The consequent synaptic triad provides an ideal configuration for dopamine modulation of glutamatergic transmission. In this issue of *Neuron*, Bamford et al. report that dopamine inhibits glutamate release in a selective manner by activating presynaptic D2 receptors.

The striatum of the mammalian brain is a large subcortical structure involved in motor coordination, cognitive functions, and disorders such as schizophrenia, drug addiction, Tourette's syndrome, Huntington's disease, and Parkinson's disease (Wilson, 2004). As the main input target for the basal ganglia, the striatum receives massive convergent innervation. The dorsal striatum receives its main excitatory glutamatergic inputs from sensorimotor cortical areas (Haber et al., 2000). There also are extremely dense dopaminergic afferents arising in the substantia nigra pars compacta and the ventral tegmental area. The striatum has been proposed to process and expedite information flow from various cortical and limbic inputs out to targets that generate appropriate behaviors (Grace, 2000). The striatum works as a gateway, filtering out unwanted impulses and maintaining smooth information flow in the cortico-striatal-thalamocortical neuronal network. A dysfunctional striatum may disrupt salient signals and pass unwanted impulses, leading to inappropriate behaviors and emotions.

The vast majority of striatal neurons are GABAergic medium spiny projection neurons. Mesostriatal dopamine (DA) afferents and corticostriatal glutamate afferents often synapse onto the same dendritic spines of the medium spiny neurons (Figure 1). This anatomical arrangement suggests a presynaptic interaction because DA often spills out of its synaptic cleft into the surrounding extracellular space (Sesack et al., 2004). Thus, this synaptic triad may be a crucial element in the striatum's regulation of glutamatergic cortical information flow.

In this issue of *Neuron*, Bamford et al. (2004) examined the functional influence of DA over glutamate release from corticostriatal terminals. Their data from mouse brain slices indicate that DA selectively inhibits particular subsets of corticostriatal afferents via activation of D2 receptors on the glutamatergic presynaptic terminals. The study was a technical tour de force, combining optical measures of glutamate release, real-time electrochemical measures of DA release, and electrophysiolog-

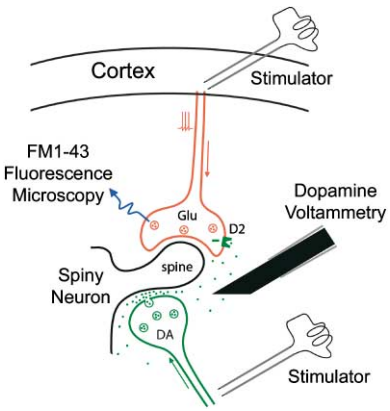

Figure 1. A Corticostriatal Glutamate Terminal and a Mesostriatal Dopamine Terminal Converge to the Same Spine of a Medium Spiny Projection Neuron

The cortical synaptic terminal is filled with FM1-43 to monitor the vesicular release of glutamate using fluorescence microscopy. Glutamate release is evoked by electrical stimulation in the cortex. Dopamine release is evoked by electrical stimulation in the striatum and is monitored by voltammetry or amperometry using a carbon-fiber electrode.

ical measures of glutamatergic synaptic activity. Corticostriatal afferents were loaded with the dye FM1-43, revealing individual fluorescent synaptic terminals (Figure 1). The rate of dye destaining, which is a measure of vesicular glutamate release, depended on the frequency of cortical stimulation. Higher-frequency stimulation of the corticostriatal afferents increased the rate of glutamate release and, thus, increased the rate of destaining. To assess the influence of DA, local striatal stimulation or bath application of amphetamine was used to evoke endogenous DA release. DA inhibited corticostriatal glutamate release from some terminals. The effect was prevented by sulpiride, a D2 receptor antagonist, and was mimicked by quinpirole, a D2 agonist, but D1 compounds did not alter glutamate release. In addition, corticostriatal destaining in D2 receptor knockout mice ($D2R^{-/-}$) was not sensitive to DA or D2 receptor agonists. These results indicated that D2 receptor activity mediated DA's influence. Electrophysiological measures suggested that the D2 receptors were located on the corticostriatal presynaptic terminals.

Because of the thoughtful experimental design, the results contained another (more interesting) level of information. Previous anatomical evidence indicated that D2 receptors are located on some corticostriatal terminals (Wang and Pickel, 2002). Because it is well known that D2 autoreceptors on DA terminals inhibit DA release (Missale et al., 1998), it was not surprising that D2 receptors located on corticostriatal terminals inhibited glutamate release. The study by Bamford et al. went beyond that result. The DA inhibition of glutamate release was minimal with low-frequency cortical stimulation, but grew much stronger with cortical stimulation at 10 Hz or higher. Low-frequency corticostriatal signals passed as usual, but high-frequency corticostriatal signals were attenuated. Furthermore, the DA inhibition was selective for terminals with a low probability of release. The more slowly a terminal destained (released glutamate) in response to cortical stimulation, then the more strongly DA inhibited the release. Although high-frequency stimulation more effectively evoked release, it was during brief high-frequency stimulation that DA caused the greatest inhibition. Thus, DA acts as a low pass filter, but the filtering is applied selectively to terminals with a low probability of release. The most important salient signals are often sent in brief bursts because bursts have a high probability of successful transmission. This presynaptic DA mechanism, however, prevents low-probability corticostriatal synapses from experiencing the higher release probability arising from afferent bursts. For a subset of corticostriatal terminals that possess D2 receptors, if there is coincident activity along nearby DA afferents, then that subset of low-probability synapses will not be as likely to transmit their salient information. It is as if the midbrain DA system has veto power over some cortical signals to the striatum.

The overall impact of DA on afferent drive and striatal output is complex, and the literature on this topic is not always internally consistent (Nicola et al., 2000). In an interesting review, Horvitz (2002) integrates the literature supporting the hypothesis that DA enhances strong concurrent glutamatergic afferents while reducing the weak inputs. Medium spiny neurons in vivo, at least under some circumstances, undergo shifts in their membrane potential (Wilson, 2004). Those neurons transition from a hyperpolarized "down state" to a depolarized "up state" from which they can send efferent output. Some evidence indicates that postsynaptic D1 receptors enhance excitation-evoked responses from spiny neurons while in the up state but diminish responses to excitation from spiny neurons in the down state (Hernandez-Lopez et al., 1997). Thus, concurrent DA activity boosts the effective excitatory drive onto spiny neurons that are already the most capable of sending efferent output, but DA makes it more difficult to excite those in the down state. The postsynaptic D1 receptor activity also increases NMDA responses at glutamatergic synapses (Flores-Hernandez et al., 2002). By boosting NMDA signals, DA selectively enhances glutamatergic inputs onto cells only when they receive strong excitation. The presynaptic DA mechanism revealed by Bamford et al. neatly fits into the point of view that DA does not help the weak. DA prevents corticostriatal synapses that are weak (i.e., have a low probability of release) from capitalizing on afferent bursts that should boost successful transmission. The complex geometry of glutamatergic and dopaminergic afferents produces a moment-to-moment interaction that ensures the proper flow of information. Part of that process in the striatum includes presynaptic D2 receptors and postsynaptic D1 receptors working synergistically to boost strong signals and dampen weak ones.

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Splitting the Spotlight of Visual Attention

Can the brain attend to more than a single location at one time? In this issue of *Neuron*, McMains and Somers report psychophysical and fMRI evidence showing that subjects can attend to two separate locations concurrently and that divided spatial attention leads to separate zones of attentional enhancement in early visual cortex.

Story has it that Elvis Presley enjoyed watching three TV programs at once. He bought three television sets, lined them up along the wall of the TV room in the Graceland mansion, and tried his best to monitor three different shows simultaneously (Figure 1). However, many scientists would argue that such feats of divided attention are impossible, even for the King of Rock 'n' Roll.

According to the spotlight theory of visual attention, people can attend to only one region of space at a time (Eriksen and St James, 1986; Posner et al., 1980). This metaphor of attention as a spotlight assumes a limited degree of flexibility. People can shift their spotlight of attention from location to location, independent of eye position, and adjust the size of the attended region like a zoom lens. However, the theory assumes that the attentional spotlight cannot be divided across multiple locations. If more than one object must be attended to at a given time—say multiple football opponents coming in for the tackle—then attention must serially shift from one location to another. The longstanding notion that spatial attention cannot be divided stems from the assumptions of early philosophers, such as Descartes, that consciousness itself is unitary and indivisible.

In this issue of *Neuron*, McMains and Somers (2004) challenge this longstanding notion by using fMRI to test whether attending to two separate locations leads to separate regions of neural enhancement in early retinotopic visual areas. The experimental design can be better understood in simplified form by considering Elvis's TV room (Figure 1). If subjects must fixate the middle TV while selectively attending to the TVs to the left and the right, what happens in visual cortex? (In the display from McMains and Somers, the "TVs" consisted of rapid serial sequences of letters and digits presented independently in the left and right locations and a task-irrelevant sequence of digits presented at fixation; the subject's task was to identify matching digits in the left and right locations.) According to the attentional spotlight hypothesis, attention cannot be divided and must spread across the middle region to encompass both the left and right stimuli. Instead, however, McMains and Somers found that attending to the separated left and right stimuli led to greater fMRI activity in corresponding retinotopic regions than when the stimuli were ignored or passively viewed, and critically, no attentional enhancement was found for the central foveal stimulus. These spatially separated attentional effects were pervasive throughout retinotopic visual cortex and were evident as early as primary visual cortex (V1).

The results provide neural evidence that subjects can attend to two separate regions of space and selectively modulate early visual activity in a top-down fashion. Perhaps, however, subjects were achieving this apparent split of attention by rapidly shifting a single spotlight from one location to the other.

To address the issue of attentional shifting, the authors performed a separate psychophysical study in which subjects viewed similar displays of letter/digit

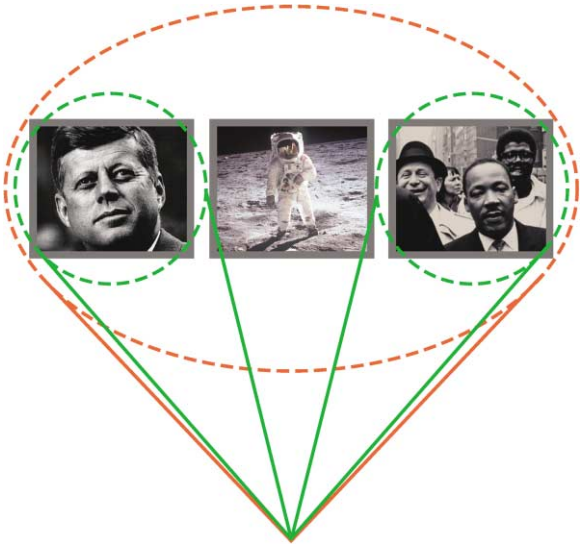

Figure 1. Schematic Diagram of Elvis's TV Room

According to the spotlight theory of attention, when subjects attend to the left- and rightmost items, attention must encompass the intervening region because the spotlight of attention cannot be divided (shown in red). Here, McMains and Somers show that subjects can attend to the left and right items independently (shown in green) while ignoring the intervening item and that this leads to separate regions of attentional enhancement in visual cortex.