treated with opioids such as morphine, despite the numerous side effects. The ability of dynorphin A to bind to a nonopioid receptor may provide new avenues for therapeutic intervention. Dynorphin A and bradykinin show little, if any, sequence homology. Together with the switch from $G\alpha_q$ to $G\alpha_s$ coupling, this indicates that these two peptides may perhaps act at different sites on the B2 receptor, sites that may be allosterically coupled. By contrast, the observation that the competitive bradykinin receptor antagonist HOE 140 interferes with both bradykinin and dynorphin A–mediated activation would be consistent with overlapping receptor binding sites. Clearly, the exact mechanism of dynorphin A activation of bradykinin receptors will need to be dissected in the future. Another interesting question is whether other endogenous and exogenous opioids can similarly act on bradykinin receptors. In terms of drug discovery, any new opioid-like compound should be assayed for potential actions on bradykinin receptors. Conversely, it may be possible to design compounds with both agonist activity on opioid receptors and antagonist activity on bradykinin receptors. This would provide for activation of opioid receptors, which mediates analgesia, while counteracting the pronociceptive effects of elevated dynorphin A levels that occur during chronic pain. Hence, the discovery of dynorphin A's unexpected action on bradykinin receptors may ultimately yield new strategies for the development of more effective analgesics.

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Stabilizing the visual world

Douglas P Munoz

Sensory systems are thought to use an internal copy of motor commands to determine which sensations are caused by the self versus the world. A new paper proves that an identified pathway performs this function for eye movements.

We actively explore our visual nvironment with rapid eye movements called saccades approximately three times per second. With each saccade, objects of interest are repositioned on the retina, but we still experience perceptual constancy. How does the brain know that the change in retinal location of an object is due to movement of the eyes and not to real motion of the object? One possibility is for sensory systems to monitor an internal copy of movement commands called corollary discharge[1–3]. In this way, the brain knows when changes in sensory responses are due to self motion, as opposed to real changes in the environment. The corollary signal from the saccadic motor command could be combined with existing visual signals to predict or anticipate the future retinal location of visual objects. However, until now there has not been an empirical demonstration of how corollary discharge is used to remap visual signals during saccades.

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A recent study in *Nature* by Sommer and Wurtz[4] has shown that corollary discharge is used to update sensory representations, by demonstrating a direct causal link between corollary discharge and updated visual processing after an eye movement. Specifically, they have identified a pathway in the brain that is critical for spatial updating of the visual world after self motion. There are neurons in the mediodorsal nucleus (MDN) of the thalamus that relay corollary discharge of saccades from the midbrain superior colliculus (SC) to the cortical frontal eye field[5,6] (FEF; **Fig. 1a**). The integrity of this pathway is critical for visually responsive neurons in the FEF to spatially shift their visual receptive fields in anticipation of the consequences of a saccade[4].

To fully appreciate the new findings[4], we need to first consider several recent observations. The first clue that anticipatory remapping of visual responses might occur came from monitoring the activity of neurons in a region of the monkey posterior parietal cortex called the lateral intraparietal area (LIP)[7]. Neurons in LIP are responsive to visual stimuli in a particular spatial location, but a subset of these neurons alter their spatial visual processing just before a saccade. Specifically, right around the time of a saccade, some LIP neurons shift their visual receptive field to a new location—where the receptive field will be located after the saccade is completed. To demonstrate this anticipatory remapping, a visual probe was presented before, during or after a saccade. Before the saccade, neurons encoding the retinal location of the probe were activated in LIP. However, around the time of the saccade, these neurons stopped responding to the probe and a new population of neurons at the anticipated new retinal location of the probe became active, even without a stimulus and before completion of the saccade. In other words, the second population of LIP neurons that became active did so before information could arrive by way of traditional visual afferent pathways to inform them of a probe in their response field[7]. This anticipatory remapping seems to be a general feature of brain areas engaged in higher visual processing, and such phenomena occur in extrastriate cortex[8], posterior parietal cortex[7], frontal cortex[9] and superior colliculus[10]. Until now, however, the precise mechanism for the remapping of visual responses during saccades has remained unknown, although it was speculated to be due to corollary discharge signals arising from self movement. Thus, a critical question is which brain structure(s) are required for providing corollary discharge to the visual areas of the brain.

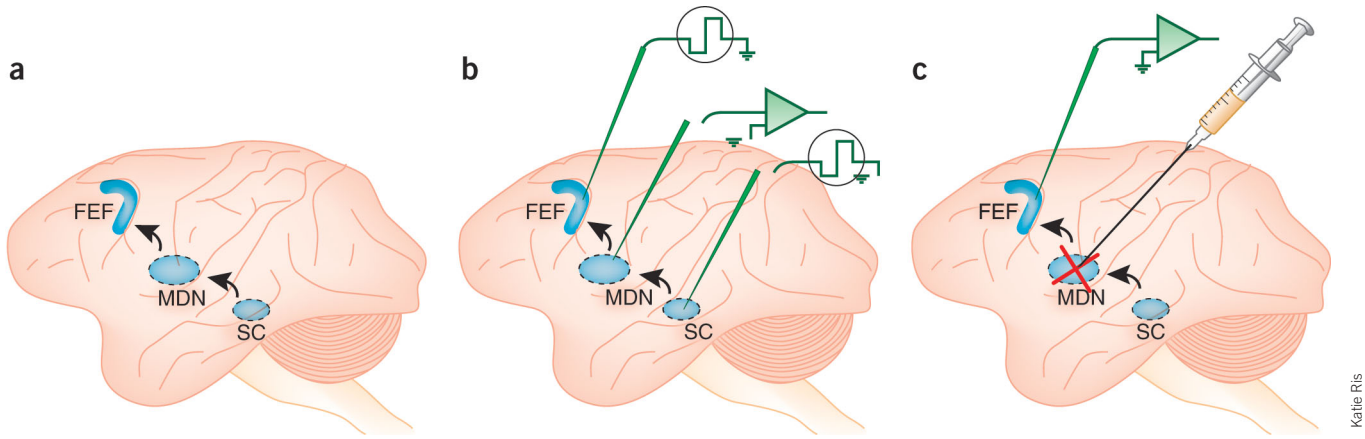

Figure 1 Pathway for collary discharge to modify visual representation. (**a**) Lateral view of the monkey brain showing the connection from the SC in the midbrain to the MDN of the thalamus and then to the FEF that is believed to convey corollary discharge from the SC to the FEF. (**b**) Placement of electrodes to demonstrate connectivity in the SC-MDN-FEF pathway. (**c**) Experiment performed by Sommer and Wurtz[4] to demonstrate the role of corollary discharge in receptive field updating in the FEF (see text for details).

Researchers hypothesized that this anticipatory remapping of visual responses would require a corollary of the motor signal to be combined with visual signals to anticipate the consequences of the saccade[7]. When the brain initiates the saccade, an internal copy of this motor command could be used to update visual representations and provide the stable percept. The SC-MDN-FEF pathway may provide the neural substrate for delivery of this corollary from the brainstem saccade-generating network to the cerebral cortex, because the SC participates in the generation of the motor command to move the eyes[11] and also provides an input to the FEF by way of the MDN of the thalamus[5].

Sommer and Wurtz[4,6,12,13] have been studying the functional role of the SC-MDN-FEF pathway systematically in monkeys using classical electrophysiological techniques of orthodromic and antidromic activation with microstimulation[14] to identify the individual neurons in this pathway. First, they recorded from neurons in the intermediate layers of the SC and microstimulated the thalamic MDN to backfire (antidromically activate) SC neurons that project an axon directly to MDN. Then, they recorded from neurons in the FEF and microstimulated the SC to reveal short-latency synaptic inputs (orthodromic activation). Finally, they recorded from neurons in MDN that received a short-latency orthodromic input after microstimulation of the SC (**Fig. 1b**). These same MDN neurons were antidromically activated by microstimulation of the FEF. Thus, the MDN neurons provide the substrate for connecting the SC to the FEF.

To test the hypothesis that this pathway from SC-MDN-FEF carries a corollary discharge concerning saccades into the contralateral visual field, Sommer and Wurtz deactivated neurons in the MDN relay by microinjecting the $GABA_A$ agonist muscimol[12,13]. Such an injection artificially inhibits the MDN relay neurons and prevents SC saccade signals from influencing the FEF. After deactivation of MDN neurons with muscimol, monkeys could still make saccades, but they failed to correctly localize targets that appeared during prior fixations, owing to an inability to account for the exact trajectory of each saccade. The interpretation of this observation is that deactivation of MDN disrupted the distribution of corollary discharge to the FEF.

Now Sommer and Wurtz[4] have gone on to perform the culminating experiment, which establishes a causal link between anticipatory receptive field shifting in FEF visually responsive neurons and transmission of the corollary signal through the MDN of the thalamus. Specifically, they demonstrated a lack of spatial remapping at the level of the FEF after deactivation of the MDN with muscimol (**Fig. 1c**). To perform the experiment, they first lowered a recording microelectrode into the FEF to identify a visually responsive neuron that had a shifting receptive field. Then, while recording from the FEF neuron, they lowered an injection syringe into MDN and quantified the amount of anticipatory remapping that was present before and after injection of muscimol. After deactivation of MDN, the visual receptive fields of neurons in the FEF failed to shift to the anticipated new location at the time of a saccade. This deficit was only observed for contraversive saccades, not for ipsiversive saccades, which makes sense because there is an SC-MDN-FEF pathway on each side of the brain, and only one of these pathways was deactivated by the muscimol injection. This latter observation shows the specificity of the deficit in targeting only the corollary signal for contraversive saccades.

For much of the past century, scientists have speculated that corollary discharge must be used to provide a stable visual percept during scanning eye movements[1–3] . Sommer and Wurtz[4] have now demonstrated that corollary discharge from the SC-MDN-FEF pathway is both appropriate and necessary to produce the anticipatory shifting in receptive fields that they observe for neurons in the FEF. Future research will be required to determine whether a similar mechanism is used to account for self-motion updating in other sensory systems. Nonetheless, it should now be possible to test directly whether the anticipatory shifting of visual receptive fields is the mechanism that produces stability in the visual world when we move our eyes.

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