

full fusion, Fernandez-Alfonso and Ryan (2004) recently reconsidered the FM studies that gave rise to the previous estimate and suggested an alternative interpretation of the data that would significantly reduce estimates of the time required for endocytosis of fully fused vesicles. In addition, a recent EGFP study (Li et al., 2005) found no evidence for preferential reuse of recently exocytosed vesicles, consistent with morphological studies showing that recently exocytosed vesicles were only slightly more likely than other vesicles to be found close to the active zone (Schikorski and Stevens, 2001). Although a kiss-and-run vesicle that remains on the surface for  $\sim 1$  s would seem to have a clear temporal advantage over a full-fusing one that lingers for  $\sim 10$  s (Gandhi and Stevens, 2003), the current results do not provide strong direct support for the hypothesis that kiss-and-run serves as an effective mechanism to speed up the rate at which vesicles become available for reuse, especially at high frequencies, when it might be expected to do the most good, and further work will be required to resolve this issue.

Another big question that still awaits an answer is whether kiss-and-run fusion affects neurotransmitter release from individual vesicles. It is an intriguing notion (and common perception) that kiss-and-run could alter the amount or time course of neurotransmitter released by a fusing vesicle, but there is little reason to think that the mode of fusion has any effect on quantal size. Direct electrophysiological measurements of miniature excitatory postsynaptic potentials under conditions that increased the likelihood of kiss-and-run fusion showed no reduction in amplitude or slowing of kinetics of unitary responses (Stevens and Williams, 2000). Although much depends on the exact characteristics of the still-undefined fusion pore, modeling estimates based on reasonable values indicate that the 400 ms time course of the briefest kiss-and-run events (Gandhi and Stevens, 2003) is well over the upper limit of  $\sim 1$  ms thought to be required for complete emptying of a glutamate-filled synaptic vesicle (see Richards et al., 2005). The possibility remains that transmitter diffuses so slowly from a kiss-and-run fusion pore that it serves only to desensitize postsynaptic receptors without ever activating them, but there is no direct evidence to date that supports this hypothesis. Further testing under conditions that promote or suppress kiss-and-run, perhaps employing cyclothiazide, a drug that blocks glutamate receptor desensitization, or  $\gamma$ -DGG, a glutamate receptor antagonist that can be used to assay transmitter concentration in the synaptic cleft, should resolve this issue in the future.

Harata et al. propose that kiss-and-run serves to conserve resources during periods of low-frequency firing and ensures that hippocampal synapses are ready to take on the demands of high-frequency activity with a full quota of fusion-competent vesicles. Whether or not this turns out to be its functional role, the current study significantly extends our appreciation for kiss-and-run as the dominant mode of fusion at these synapses and identifies frequency of stimulation as a factor that can modulate the prevalence of kiss-and-run. In addition, Harata et al. have provided researchers in the field with powerful new tools to address those issues that remain unresolved.

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## Flick-Induced Flips in Perception

**Microsaccades are miniature eye movements produced involuntarily during visual fixation of stationary objects. Since their first description more than 40 years ago, the role of microsaccades in vision has been controversial. In this issue, Martinez-Conde and colleagues present a solution to the long-standing research problem connecting this basic oculomotor function to visual perception, by showing that microsaccades may control peripheral vision during visual fixation by inducing flips in bistable peripheral percepts in head-unrestrained viewing. Their study provides new insight into the functional connectivity between oculomotor function and visual perception.**

Information processing of stationary visual targets is restricted to periods during which the eyes appear to be at rest, a state called *visual fixation*. However, fixation is in reality a highly dynamic oculomotor process featuring a surprising panoply of involuntary and unconscious miniature eye movements. In the 1950s, experimental suppression of these movements in a paradigm called *retinal stabilization* was reported to induce *perceptual fading* (Ditchburn and Ginsborg, 1952; Riggs et al., 1953), leading to the hypothesis that the three major “fixational” eye movements—microsaccades, drifts, and tremors—are generated actively by the oculomotor

plant to counteract perceptual fading caused by retinal adaptation. However, while microsaccades represent the largest and fastest component of fixational eye movements, their specific functional role in vision during visual fixation could not be definitively proven at that time. Therefore, many researchers concluded that microsaccades were experimental anomalies confined to specific viewing conditions with artificially restrained heads (Steinman, 2003) with no specific role in vision, and this controversy continued over several decades (Martinez-Conde et al., 2004).

Taking advantage of advances in eye-movement-tracking technology unavailable to earlier researchers, Martinez-Conde et al. (2006) recorded the eye movements of participants viewing the Troxler illusion, devised in 1804 and involving a visual field consisting of a central spot surrounded by a peripheral annulus which then appears and disappears from perception during visual fixation on the central spot (see Figure 1 of Martinez-Conde et al., 2006). The authors used this effect to investigate whether the occurrence of microsaccades modulates fading of a peripheral gabor patch. It is surprising that this critical and simple experiment on the role of microsaccades for perception of peripheral targets has never been carried out before.

Martinez-Conde et al. first asked participants to fixate on the central spot and continuously report their perception of the peripheral target annulus. Under these conditions, a bistable visual state is induced, flipping between fading and intensifying perception of the target stimulus. Analysis of these results revealed that perceptual flips were correlated with microsaccades (also termed “flicks” in early work): the probability, rate, and magnitude of microsaccades decreased before transitions to a fading epoch and increased before the opposite transition to an intensifying percept. In a calculation of the contribution of microsaccade rates to visibility of the percept, the authors estimated that 60% of the perceptual flips from fading to intensifying were preceded by one microsaccade more than expected by chance. Moreover, microsaccade amplitude turned out to play a role, too, because even in the absence of rate effects microsaccade amplitude variations induced perceptual transitions. The results provide the first experimental demonstration of a specific perceptual function for microsaccades in vision.

A frequent concern for the significance of microsaccades in natural vision is that the experimental conditions used to measure them typically involve head-restrained viewing (Steinman, 2003). The argument behind this critique is that postural sway should provide sufficient retinal image slip, so that microsaccades would be dispensable for free viewing. To rule out this possibility, Martinez-Conde et al. showed that their key finding is still valid under head-unrestrained viewing. This result is supported by a theoretical argument comparing the statistics of postural sway and fixational eye movements. Fluctuations in postural sway follow a highly specific pattern of correlations with persistent motion (i.e., the movement trajectory has the tendency to sustain its current direction) on a short timescale and antipersistent motion (i.e., the trajectory has the tendency to reverse its current direction) on a longer timescale (Collins and De Luca, 1993). Interestingly, the presence

of the same qualitative type of correlated random motion can be observed in fixational eye movements (Engbert and Kliegl, 2004), but the transition point between short and long timescales is much smaller for fixational eye movements than for postural sway. If we assume that the pattern of correlations in fixational eye movements is functional, then postural sway cannot replace fixational eye movements in driving retinal image motion adequately for the perceptual needs underlying free vision.

Recent progress on fixational eye movements and microsaccades has been made possible by enormous improvements in eye-tracking technology and a simplification of experimental procedures (e.g., Engbert and Kliegl, 2004). For example, using high-precision recording of fixational eye movements during psychophysical tasks like attentional cueing (Hafed and Clark, 2002; Engbert and Kliegl, 2003), microsaccade orientations were exploited to map the time course of spatial attention. The current findings by Martinez-Conde et al. suggest that these variations in microsaccade dynamics may be functional for enhancement of visual processing of information in the periphery of the visual field. Future studies using these approaches are expected to reveal insight into the potential two-way communication and coordination between attentional dynamics and fixational eye movements.

Researchers have also found microsaccade modulation of neural activity in several areas in the visual pathway, including excitatory bursting activity in primate area V1 (Martinez-Conde et al., 2000) and also in the LGN (Martinez-Conde et al., 2002; Reppas et al., 2002). Responses in both V1 and LGN are visual rather than oculomotor, because if stimuli were removed from the recorded neuron’s receptive field, microsaccades could no longer generate neural activity. Even more surprisingly, the size of microsaccade-induced bursting activity depends on optimality of the stationary visual stimulus applied. For example, when using an optimally oriented bar of light, microsaccades induced longer bursts compared to a stimulus with nonoptimal characteristics. Microsaccades are also proposed to contribute to other visual functions, including disambiguating latency and brightness in visual perception, enhancing spatial summation by synchronizing the activity of neurons with neighboring receptive fields, and modulating temporal summation of the visual response (Martinez-Conde et al., 2004).

In summary, research on microsaccades spans a whole microcosm of phenomena in perception, attention, and oculomotor control. Martinez-Conde et al. (2006) have added impressive new evidence for the tight link between oculomotor behavior and visual perception, and the findings are expected to stimulate the development of more dynamic models for how these processes may be coordinated. On this foundation, new investigations on the neural, behavioral, and cognitive functions of microsaccade eye movements promise to reveal new insight into this fundamental property of vision.

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## Selectivity of Adaptation in Single Units: Implications for fMRI Experiments

**Understanding the neural basis of adaptation (repetition suppression) is critical for interpreting fMRI-adaptation experiments. Sawamura and colleagues provide a critical stepping-stone by elucidating the relation between neural adaptation and response selectivity. They find some cross-adaptation by two different stimuli that activate the same neuron.**

Adaptation (also referred to as repetition-suppression) reflects the phenomenon of reduced responses to repeated presentation of a specific stimulus. Adaptation effects are robust and can be measured with single-unit recordings, fMRI, and EEG and in many cortical regions, including visual areas, auditory cortex, and prefrontal cortex. Despite the robustness of adaptation effects and the increased interest in the field, the underlying neural mechanisms are not well understood. Adaptation may reflect a proportional reduction in firing rate to repetitions of a specific stimulus, change in the tuning of neural responses for repeated stimuli, or shortening of the processing time for repeated stimuli (for a recent review see (Grill-Spector et al., 2006)). In the current issue of *Neuron*, Sawamura and colleagues (Sawamura et al., 2006) present a novel study that provides an important stepping-stone for elucidating neural mechanisms underlying adaptation.

Understanding the neural mechanisms of adaptation effects is important for two main reasons: (1) adaptation has become a popular tool for characterizing functional properties of neural populations in humans with fMRI (especially given claims that it tags specific neural populations within fMRI voxels [Grill-Spector and Malach, 2001]); (2) there is a potential relation between adapta-

tion effects and behavioral priming (Schacter and Buckner, 1998; Wiggs and Martin, 1998). Priming refers to improved performance in accuracy and response time for repeated items and occurs under the same conditions as adaptation. However, recent results show that adaptation in object-selective cortex can occur without priming (Sayres and Grill-Spector, 2005) and priming can occur without adaptation in object-selective cortex (Dobbins et al., 2004), somewhat weakening previous claims that adaptation in object-selective cortex reflects behavioral priming (Schacter and Buckner, 1998; Wiggs and Martin, 1998).

In a typical fMRI-adaptation experiment, researchers measure the reduction of the BOLD response to identical repeated stimuli, the reduction of BOLD response by different, albeit related stimuli (e.g., the same object in different views) compared to nonrepeated stimuli. The finding that adaptation levels for different-related stimuli were similar to those of adaptation by identical stimuli suggests that neural populations are insensitive to the difference between the related stimuli because there was cross-adaptation. In contrast, recovery from adaptation by different-related stimuli (i.e., no cross-adaptation) suggests that neural populations are sensitive to the differences between related stimuli. However, inferring neural tuning from fMRI-adaptation depends both on the relation between fMRI (BOLD signals) and action potentials (Logothetis et al., 2001; Mukamel et al., 2005) and the relation between neural adaptation and stimulus selectivity. The underlying assumption based on previous single-unit studies (Lueschow et al., 1994) is that adaptation and stimulus sensitivity are related. The goal of the present study by Sawamura and colleagues was to directly examine the relation between selectivity and adaptation level of single neurons in monkey inferotemporal (IT) cortex.

The current study follows a previous study from the same group (Sawamura et al., 2005), in which they showed that adaptation effects measured with fMRI in monkey IT are similar to adaptation effects measured with fMRI in human lateral occipital complex (LOC) (Grill-Spector et al., 1999). Measuring adaptation effects in the same cortical region and similar experimental designs with different methods (single-cell physiology and fMRI) provides a bridge between adaptation effects in neurons and fMRI within the same species. Given the similarities between fMRI-adaptation effects in human LOC and fMRI-adaptation in monkey IT, these results have implications for interpreting human fMRI-adaptation studies.

In the study presented in the current issue of *Neuron*, Sawamura and colleagues measured responses in monkey IT cells when they presented monkeys repeated items of object stimuli. They tested the effects of repetition on IT cell responses when repeating identical images that activated a cell (A-A or B-B), presenting alternating sequences of two images that activated the cell (i.e., repeats of A-B), and presenting alternating sequences of images in which the first image did not produce a significant response in the neuron (i.e., repeats of C-A). These stimuli were presented in two experiments: in the first they presented stimuli repeated up to 30 times, and in the second they presented stimuli embedded within a sequence of other nonrepeated images.