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Modulation of visual physiology by behavioral state in monkeys, mice, and flies

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When a monkey attends to a visual stimulus, neurons in visual cortex respond differently to that stimulus than when the monkey attends elsewhere. In the 25 years since the initial discovery, the study of attention in primates has been central to understanding flexible visual processing. Recent experiments demonstrate that visual neurons in mice and fruit flies are modulated by locomotor behaviors, like running and flying, in a manner that resembles attention-based modulations in primates. The similar findings across species argue for a more generalized view of state-dependent sensory processing and for a renewed dialogue among vertebrate and invertebrate research communities.

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Introduction

The cross-continental migration of the Monarch butterfly and the waggle dance of the honey bee can inspire awe. Perhaps just as remarkable as these single behaviors is the emerging realization that individual insect species perform a surprisingly large overall number of behaviors. For example, the fruit fly, *Drosophila melanogaster*, with a brain containing on the order of 100,000 neurons, flies, walks, sleeps, grooms, jumps, mates, fights, navigates, evades, chooses, and remembers (e.g. [1–4]). In other words, small-brained animals do not do a small number of things; rather, they do a large number of things with a small number of neurons. This important realization shines new light on a classic question: how do small and big brains differ [5]? In particular, when a nervous system has thousands of neurons to accomplish the many tasks of life, what are the fundamental differences in how it solves higher-order computational problems compared to a brain that has billions of neurons?

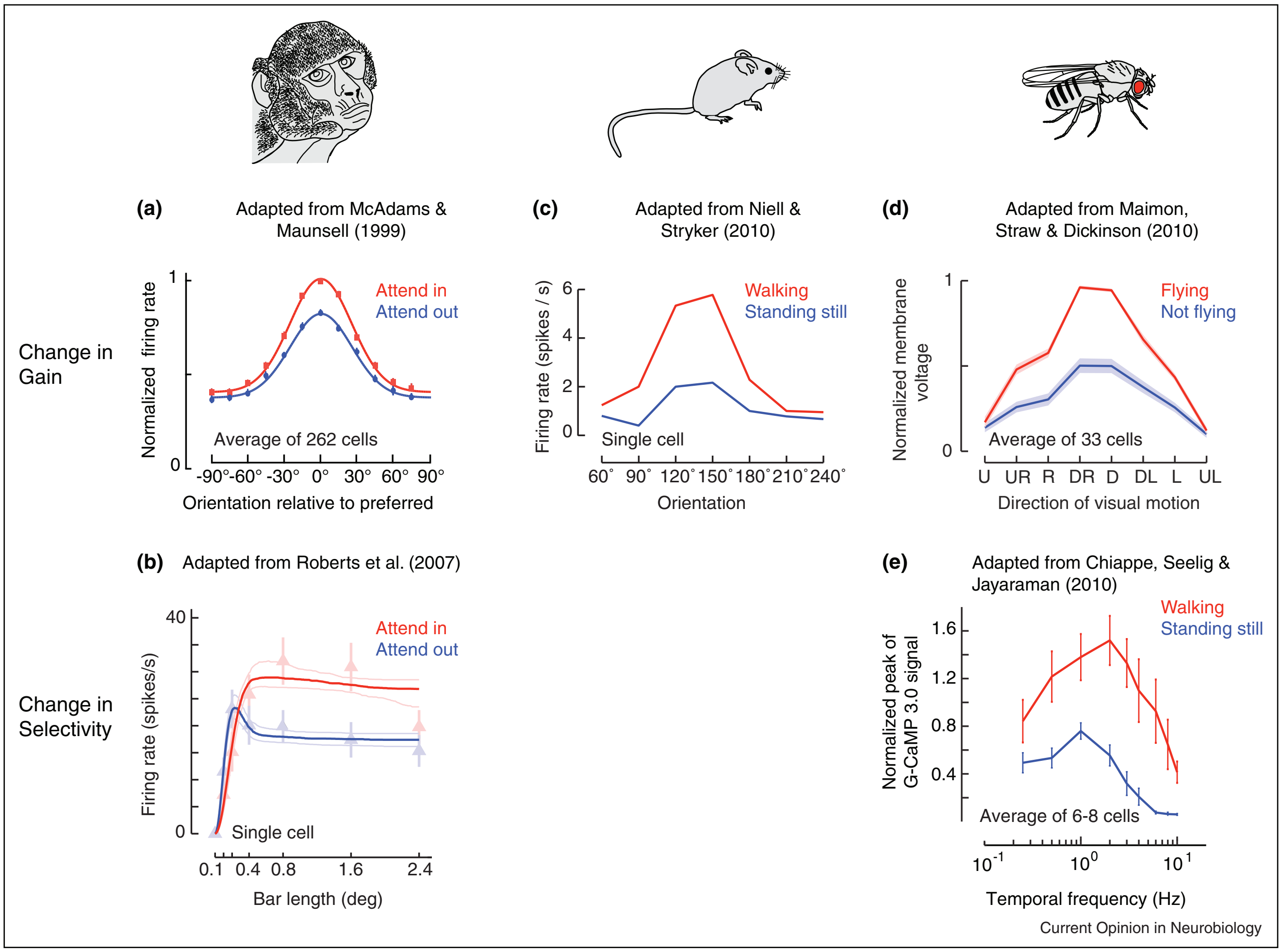
Vision provides an attractive sensory system for comparing neural computation across brain size. Visual systems in animals with small brains, like flies, and big brains, like primates, have been exceptionally well studied from molecular to behavioral levels, which helps ground comparative thinking. It is relatively easy to present similar and spatiotemporally precise visual stimuli across different preparations. Visual neurons in monkeys and flies, and probably most animals with image-forming eyes, show common response properties such as localized receptive fields, adaptation, and tuning to parameters like the direction of visual motion. For these reasons there has already been a productive interchange between monkey and fly research communities on mechanisms of motion processing and sensory-response variability, for example [6].

Here I focus on the question of how ongoing behavior modulates visual physiology. Specifically, I compare how spatial attention alters visual processing in monkeys with how locomotion modulates visual processing in fruit flies and mice. (Mice are fast becoming another prominent model system for vision.) Because spatial attention is a process that dynamically highlights one location of the visual field over others, whereas locomotion is a global motor state that does not even require eyes, comparing these two might seem odd or unjustified. It is indeed too early to tell what, if anything, is genuinely common to flying flies and attending primates. Nevertheless, I hope to highlight clear similarities in how visual neurons are modulated by attention and locomotion across species (Figure 1). Such similarities, which have only recently come to light, support the idea that cognitive factors like attention may share something with motor acts like locomotion in that they are both behavioral states, broadly defined, that can influence sensory physiology. In this view, state-dependent visual processing is not a special attribute of mammalian cerebral cortex or an idiosyncrasy of small invertebrates, but is instead a general feature of potentially all visual systems.

Spatial attention in primates

The function of a visual system is to condense and transform patterns of light into a form that is meaningful to the rest of the brain. One important aspect of this transformation is to emphasize behaviorally relevant stimuli and deemphasize irrelevant ones. It is perhaps for this reason that cortical neurons typically respond more strongly to a visual stimulus when a monkey attends to this stimulus versus attending elsewhere

Figure 1



Changes in visual-neuron tuning curves with behavioral state in three species. **(a)** Population-averaged, orientation tuning curves of single-neuron firing-rates in macaque area V4. When the monkey attends to a single stimulus in the receptive field, the tuning curve is multiplicatively boosted by a scalar at all orientations. **(b)** Single-neuron tuning curves to the length of a bar in macaque V1. When the animal attends to the stimulus, responses are stronger for long bars and weaker for short bars, thus changing the shape of the curve. **(c)** Orientation tuning curves of a single neuron in mouse V1. Responses are generally boosted when the animal locomotes on an air-supported ball. **(d)** Population-averaged tuning curves for the direction of wide-field motion in lobula-plate tangential cells (vertical-system cells) of the Drosophila visual lobe. During flight, the membrane voltage of these non-spiking cells is more depolarized in response to visual motion. **(e)** Population-averaged temporal-frequency, or speed, tuning curves in lobula-plate tangential cells (horizontal-system cells) of the Drosophila visual lobe. When the animal walks on an air-supported ball, [Ca^{2+}] responses to certain stimuli are more strongly boosted than others leading to a small shift in the peak of the curve toward faster motion speeds.

[7,8]. Concomitant with these physiological changes is enhanced behavioral performance at the attended spot; reaction times to visual events are faster and the subject's ability to discriminate fine changes in visual structure is improved [9].

A central challenge has been to determine whether attention amplifies neuronal responses to all stimuli uniformly or whether certain stimuli are preferentially emphasized over others. By analogy to a radio, this question is akin to asking whether attention increases the volume or tunes into a certain station. The answer appears to be that depending on behavioral task, stimulus context, cell type, and brain region, both types of effects are observed [10–14] (Figure 1a,b), emphasizing the complexity of the cerebral cortex.

What are the underlying mechanisms? Several studies suggest a top-down origin. Microstimulation of the frontal eye fields, a higher brain region that controls eye movements, can drive increased firing rates in lower visual areas in a manner reminiscent of attention-based modulations [15]. Moreover, when attention is shifted from one locus to another, the physiological manifestations are first evident in higher brain areas and only tens-of-milliseconds later appear in lower visual areas [16••,17].

Top-down signaling, however, is not the entire story. Sensory normalization is a process of local gain control, observed across sensory systems and species, where the responses of single cells are reduced in proportion to the overall activity level of the local population [18,19]. Normalization helps to prevent saturation of single-neuron responses to very strong stimuli. An intriguing recent finding is that cortical cells that are strongly influenced by normalization are also strongly influenced by attention, suggesting that attention and normalization share similar underlying mechanisms [20,21]. Pharmacologically, the neuromodulators involved in normalization and attention have not been comprehensively determined; however, acetylcholine, acting through muscarinic receptors, has been shown to boost the effects of attention in primary visual cortex (V1) [22]. Acetylcholine may serve a very general role in modulation of mammalian visual circuits [23].

An important frontier is to understand how populations of neurons, rather than individual cells, are affected by attention [24]. A surprising recent finding is that even as the firing rates of individual neurons increase, the firing-rate correlations among neighboring cells actually decrease with attention [25,26•,27•]. In other words, when an animal attends to a location in space, visual neurons that are sensitive to that location convey signals that are more independent from one another compared to the unattended state. A statistically ideal observer, extracting information from the stimulus-driven population activity, gains more from the drop in correlated firing than from the increased spike rates [26•,27•], suggesting that changes in correlation may be functionally relevant.

Why genetic model systems?

The macaque cerebral cortex contains hundreds of cell types with distinct anatomical projections, neurotransmitter complements, synaptic dynamics, intrinsic electrophysiological properties, and spiking statistics. With extracellular recording methods, one can differentiate among broad cell categories—putative interneurons and pyramidal cells, for example, which have distinct spike-waveform widths [28–30]—but it is not generally possible to consistently and unambiguously target unique cell classes for study. As a result, there remains significant unexplained variability from cell to cell in the effects of attention, with many neurons showing the opposite effect to the mean, for example.

Other model systems [31] and in particular genetic model systems could prove vital in developing a cellular-level understanding for state-dependent sensory processing. With genetic model systems, experimenters can often target defined cell populations for electrophysiology. Moreover, being able to use genetic tools to manipulate activity in specific cells, and to potentially characterize downstream and upstream circuits, could clarify the functional roles of visual modulations. In what follows, I describe contemporary work in mice and fruit flies, two emerging genetic model systems for the study of state-dependent sensory processing.

Mice in motion

An important recent discovery is that head-fixed mice can perform discrimination and valuation tasks while the experimenter records physiological activity in genetically identified neurons [32,33]. Whereas a precise behavioral analog of visual-spatial attention has not been developed for the head-fixed rodent, researchers have been able to study the effect of a different behavioral state, locomotion, on visual physiology.

Niell and Stryker (2010) performed extracellular recordings from V1 neurons of mice placed on an air-supported styrofoam ball [34••]. When a mouse transitions from standing still to running on the ball, the baseline activity and preferred orientation of V1 cells are not significantly altered, however, evoked visual responses are more than two-fold stronger (Figure 1c). This gain boost is not present in neurons of the dorsal lateral geniculate nucleus of the thalamus, the principal conduit of information from the retina to the cortex, demonstrating that the modulation is not caused by a peripheral change, such as more vigorous eye movements while running. The authors did not target any specific cell type in these initial recordings; nevertheless, they noted specificity to the cortical modulation. Cells with narrow action-potential waveforms, putative interneurons, showed an effect opposite to the mean; their firing rates were markedly suppressed by visual stimulation when the animal was running. The genetic tools available in mice should allow researchers to manipulate these putative interneurons or other specific cell types to test their precise role in visually guided locomotor behavior.

At the population level, it is not yet known whether mouse V1 cells fire in a more or less correlated fashion during locomotion. However, in elegant work on mouse somatosensory cortex—using dual whole-cell patch clamp recordings in head-fixed, behaving mice—it was found that nearby pyramidal neurons show less correlated fluctuations of their membrane voltage during active movement of the whiskers compared to quiet wakefulness [35], an effect reminiscent of the drop in correlated spiking activity during attention in primates. Mechanistically, it appears that the somatosensory cortex may switch from a mode where parvalbumin-positive, fast-spiking inhibitory interneurons globally control the network during quiet wakefulness [36] to a state where the network is more decentralized during active behavior.

Visual physiology in behaving fruit flies

Invertebrates have long been essential for the study of vision [37] and neuromodulation [38]. Flies, in particular, have one of the best characterized visual systems in the animal kingdom [39], and the vision-based behaviors of genetic model organism *Drosophila melanogaster* have been extensively documented in recent years. While there is currently no database of all the cell types in the *Drosophila* brain—this is in the works [40]—it is now possible to target scores of defined cell populations for genetic manipulation and physiology [41,42•] with relative ease.

The lobula complex is the final stage of processing in the fly visual lobe. It houses the well-studied lobula-plate tangential cells, which are motion-sensitive neurons important for stabilizing flight [43,44]. Early work led to the view that tangential cell physiology is stereotyped and not dependent on behavioral state [45]. To test this hypothesis, we developed a preparation for whole-cell patch clamp recordings in behaving *Drosophila* [46]. Tangential cells were recorded in animals that were attached to a platform but free to flap their wings in tethered flight. In opposition to stereotypy, we found that lobula-plate tangential cells show a doubling of their visual responses when flies are flying compared to when they are not flying (Figure 1d)—a gain modulation reminiscent of those observed in primate and rodent brains (Figure 1a,c).

Because we could repeatedly perform whole-cell recordings from tangential neurons, we were also able to test a specific mechanism for this modulation. By Ohm's law, the larger a cell's membrane resistance the more its membrane voltage changes for a given synaptic current. Thus, one way to implement a gain boost is for a cell to increase its membrane resistance by closing ion channels typically open on its membrane. Contrary to this model, we found that the membrane resistance of tangential cells actually decreases during flight, owing to a flight-specific conductance whose origin is still not completely clear [47]. Thus to achieve boosted sensory responses, the electrically leakier cells probably receive stronger synaptic drive from upstream visual neurons.

Whereas our experiments on flying flies tested the motion-direction tuning of tangential cells, another recent study, by Chiappe *et al.* (2010), measured the speed, or temporal-frequency, tuning of these neurons [48•]. The authors imaged intracellular [Ca^{2+}] with two-photon microscopy while the animals walked on a tiny air-supported ball. Like with mouse V1 cells, responses of fly visual neurons are stronger when the animals actively walk on a ball, but the response enhancement is not uniform. Walking preferentially boosts stimuli at high temporal frequencies over low frequencies, which causes the tuning curve to change shape (Figure 1e). The functional significance of this shape change is not yet known; however, because the peak of the curve shifts toward higher frequencies, this modulation may help flies process faster visual motion associated with locomotion.

When an agonist of octopamine, a biogenic amine that is released broadly for insect fight-or-flight behavior, is applied to the blowfly lobula plate, one observes a boost in tangential cell visual responses [49], and this boost is dependent on the temporal-frequency of the stimulus [50]. Thus, release of octopamine may serve an important role in modifying visual physiology for locomotion in flies, much like acetylcholine serves to modulate visual processing in mammals. These two modulators, both acting through G protein-coupled receptors, may be just the tip of the iceberg with regard to visual neuromodulation. Future studies should seek a systematic analysis of the chemical influences on visual computation in behaving animals.

Conclusions and perspectives

Naïvely, one might have imagined that small-brained mice or tiny-brained insects would show highly stereotyped visual physiology. However, monkeys, mice, and flies actually exhibit similar state-dependent modulations in visual activity, with alterations in response gain and stimulus selectivity now documented (Figure 1). Thus, modulation is a common feature of visual computation, not something that distinguishes brains with billions of neurons from brains with thousands of neurons.

To invertebrate researchers, this conclusion is not likely to be surprising. Some of the best studied modulated circuits, outside of the visual system, are numerically tiny invertebrate networks. For example, the stomatogastric ganglion of crustaceans contains about 30 cells and is recipient to over 20 modulatory substances, each of which predisposes the network to a different pattern of activity [51]. To what extent do lessons from the stomatogastric ganglion, a small motor circuit for digestion, generalize? The data presented here suggest that extensive modulation may be a property of many visual systems as well. It may be that neural networks with reduced numbers multiplex several functions onto the same cells and thus actually show more behavioral-state modulation than larger networks. Indeed, extensive modulation may be one of the secrets behind how small organisms achieve so much with so little. Alternatively, primates might show similarly high levels of modulation, waiting to be discovered.

A hallmark of spatial attention is that perception is affected at one location of the visual field, not others. A change in locomotor state, on the contrary, yields a broad enhancement of visual processing. Thus, experiments in genetic model systems cannot yet illuminate how the brain selects one location in the visual field for special processing, which is one of the great unsolved problems of spatial attention. However, it is possible that mice, and perhaps even insects [52,53], selectively attend to stimuli. With the advent of more sophisticated behavioral-physiology paradigms, one may be able to address attention-like phenomena in these species. Because mice and fruit flies do not have a fovea, the results of such experiments may reveal the extent to which spatial attention is critically linked to foveating eye-movements, a central unresolved issue. Conversely, studying more ethological behaviors in monkeys, like locomotion, might reveal novel, unexplored modulations of primate visual cortex.

With so many examples of visual modulation now documented, the highest priority is to determine their function. Nervous tissue is metabolically expensive [54]. One potential reason for having a gain knob on a sensory system is to turn the system down or off so as to save energy when it is not in use. Future work should seek to determine if visual modulations are, at least partly, present for energetic considerations, and not just to generate reaction-time and discrimination benefits associated with typically stronger activity.

Aside from energetics, the function of sensory activity has typically been described from the perspective of an ideal observer extracting information from spike trains. However, neurons that receive and interpret visual spike trains in the brain are not guaranteed to operate anything like ideal observers. A crucial next step is to understand, at a cellular level, how modulated visual activity impacts downstream or upstream processing so as to ultimately modify behavior. The reduced cell numbers and premiere genetic tools of *Drosophila* may help in getting a first wave of answers, providing a template for how to approach this important issue in larger-brained species.

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