

Sensation during Active Behaviors

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A substantial portion of our sensory experience happens during active behaviors such as walking around or paying attention. How do sensory systems work during such behaviors? Neural processing in sensory systems can be shaped by behavior in multiple ways ranging from a modulation of responsiveness or sharpening of tuning to a dynamic change of response properties or functional connectivity. Here, we review recent findings on the modulation of sensory processing during active behaviors in different systems: insect vision, rodent thalamus, and rodent sensory cortices. We discuss the circuit-level mechanisms that might lead to these modulations and their potential role in sensory function. Finally, we highlight the open questions and future perspectives of this exciting new field.

Key words: brain state; locomotion; remapping; sensory coding; state-dependent processing; task-dependent processing

Introduction

Under natural conditions, we constantly engage our sensory systems during a myriad of everyday active behaviors: finding food, detecting threats, or exploring. Ideally, we would like to understand neural processing during such active behaviors. Indeed, when David Hubel invented the tungsten electrode, he first recorded with chronically implanted electrodes from the visual cortex of unanesthetized, unrestrained cats (Hubel, 1959). He discovered that neurons in the visual cortex fired in surprising ways: they were active even in darkness and their firing rate was modulated by arousal. However, he could not track where the cat's eyes pointed, so he could only poorly define the visual stimulus, making it difficult to characterize the neurons' receptive field (RF) properties. It was not until Hubel, together with Torsten Wiesel, used acute experimental approaches with anesthetized and paralyzed animals to obtain exquisite control of sensory

stimulation parameters and improved recording stability that they could make their transformational discoveries on RF properties along the early visual system (Hubel, 1982; Wiesel, 1982).

The acute approach led to extremely successful and powerful notions of a hierarchically organized brain with neurons that serially extract behaviorally relevant features (Hubel and Wiesel, 1998). However, converging lines of recent evidence suggest that cortical neurons receive multiple input types, each capable of eliciting action potentials. For example, context-dependent remapping of representations is commonly observed in the hippocampus (Muller and Kubie, 1987), prefrontal cortex (PFC), and posterior parietal cortex (Leutgeb et al., 2004; Azañón et al., 2010; Hall and Colby, 2011; Zirnsak et al., 2014), suggesting that RF properties can be dynamic and variable.

The variability of RF response properties can also be related to changes in activity states that occur during wakefulness (Harris and Thiele, 2011; McGinley et al., 2015b). In recent years, how such active states influence sensory responses has received considerable attention, fueled by the broad application of methods allowing locomotion despite head fixation in combination with cellular resolution large-scale population imaging, high-density electrophysiological recordings, and detailed genetic perturbation approaches. These advances allow the study of both behavioral-state-dependent processing and sensorimotor integration and navigation.

Here, we review emerging shifts in our understanding of neural processing during active, multidimensional behavior in different systems (fly vision, rodent somatosensation, vision, audition) and at different processing levels (fly lobula plate, mammalian thalamus, and cortex). We discuss the potential sources of these behavior-dependent modulations with particular focus on the role of neuromodulators and inhibitory in-

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terneurons, followed by examples of the potential function of such modulations in movement control, object detection, navigation, and attentional tasks. We conclude by addressing open questions and promising directions for future research.

Visual motion processing during active behaviors in the fly

We begin this review where this field first took shape (Buchner, 1976): the fly visual system. In flies, vision is critical for the control of active locomotor behavior; without it the capacity to maintain a straight course is jeopardized (Souman et al., 2009; Robie et al., 2010). A prevailing idea is that optic flow, the pattern of image flow generated by movement, is actively used to steer the body (Srinivasan, 2001; Borst, 2014). Consistent with this idea, the fly visual system has cells with activity that is tuned to optic flow generated by specific movements: horizontal system (HS) cells to rotations along the yaw and vertical system (VS) cells along the pitch or roll body axes (Krapp et al., 2001; Borst, 2014; Silies et al., 2014). Both HS and VS cells, which are found across different flying species, are direction selective and tuned to a preferred velocity of the visual stimuli (Hausen, 1982; Joesch et al., 2008; Schnell et al., 2010). Because movement of the body through air results from the combined effect of the moving medium (airflow) and the animal's locomotion, visual-flow-sensing mechanisms are considered critical for steering control (Chapman et al., 2011). Accordingly, HS and VS cells are thought to be part of a stability reflex system that compensates for unintended body movements due to airflow (Hausen and Wehrhahn, 1990).

Explorative locomotion displays typical paths structured by segments of stable course, referred as fixations, interrupted by rapid changes in course direction, referred as saccades (Schilstra and Hateren, 1999). Recordings performed in HS and VS cells under fixations have shown that flight shifts the cells' temporal tuning toward high stimulus velocities (Jung et al., 2011; Suver et al., 2012). In addition, flight increases HS and VS cells' response magnitude to visual stimuli (Maimon et al., 2010; Schnell et al., 2014). In striking contrast to these modulations, saccades suppress visual responses in HS cells such that their direction-selective responses are attenuated (Schnell et al., 2014; Kim et al., 2015). The suppressive impact of saccades in VS cells scales with the expected response amplitude that a saccade-induced visual stimulus would generate (Kim et al., 2017). Therefore, flight flexibly tunes the gain and the temporal processing characteristics of an optic-flow-sensitive network to accommodate the physiological requirements imposed by behavior.

In contrast to other fly species, in *Drosophila*, walking is as important as flight because courtship in this genus occurs on terrain. The first indication that behavior modulates the velocity tuning of HS cells was in fact observed in head-fixed flies walking on an air-suspended ball (Chiappe et al., 2010). Similar to flight, HS cells' visual responses are enhanced when walking, scaled monotonically with speed (Chiappe et al., 2010; Longden et al., 2014). Even when walking in the dark, HS cells are modulated by three distinct, nonvisual signals (Fujiwara et al., 2017). First, there is a nonspecific signal that depolarizes HS cells before the onset of walking, grooming, or jumping, and outlasts the termination of any of these behaviors. Second, turning and forward walking modulate HS cell activity. Finally, the direction of turning can excite or inhibit a given HS cell and always complements the direction of visual motion to which the neuron is tuned (Fujiwara et al., 2017). When HS cells are stimulated visually in walking flies, the response dynamics of the cells encode the combined visual and turning velocities rather than their difference. As a result, during fixation, HS cells encode the leg-based turning of

the fly faithfully even without visual input. This cooperative interaction between leg-based turning and visual velocities during fixations may be used to compute a calibrated estimate of self-motion (Gu et al., 2008), suggesting that HS cells operate as self-movement estimators rather than error detectors during walking.

In summary, behavior induces modulations in optic-flow-processing cells that are common to stable flight, saccading flight, and walking, and are also behavior specific. The modulation in responses seems to be consistent with behavior-specific specializations: self-motion estimation while walking, error correction during stable flight, and visual suppression during saccadic flight. It remains unclear whether this behavior-specific specialization is related to the medium through which the fly moves. Future work must synthesize the plethora of phenomenon described here. For this, it will be critical to identify how and where the behavioral-related and visual signals are integrated within the optic-flow-processing network.

Active behaviors modulate neural processing in rodent sensory cortex

In rodents, the active state has been defined predominantly on the basis of three parameters: whisking, locomotion, and pupil dilation.

Somatosensory cortex

There is a long tradition of studies investigating state-dependent neural processing in the rodent somatosensory cortex, in which whisking has been used as indicator of active state. Pioneering studies using whole-cell patch-clamp recordings in primary somatosensory cortex (barrel cortex, S1) of awake mice revealed that, when mice explore their immediate environment actively by rhythmic whisking, S1 layer 2/3 (L2/3) excitatory neurons significantly reduce slow-wave membrane potential fluctuations and depolarize slightly (Crochet and Petersen, 2006; Poulet and Petersen, 2008; Gentet et al., 2010). In the active behavioral state, sensory responses of S1 L2/3 neurons to passively applied whisker stimulation are small (Crochet and Petersen, 2006). When mice palpate an object actively with their whiskers, however, individual whisker–object contacts (active touches) evoke robust sub-threshold sensory responses (Crochet and Petersen, 2006; Crochet et al., 2011), inducing spikes in a subset of S1 neurons (O'Connor et al., 2010; Crochet et al., 2011; Peron et al., 2015) that are essential for perception of touch (O'Connor et al., 2013).

During whisker-related somatosensation, active behaviors influence S1 L2/3 excitatory neurons differentially and in a projection-specific way (Yamashita et al., 2013). S1 L2/3 contains excitatory neurons projecting either to ipsilateral secondary somatosensory cortex (S2) or ipsilateral whisker primary motor cortex (M1) (Aronoff et al., 2010). These S2-projecting (S2-p) and M1-projecting (M1-p) neurons are spatially intermingled, largely nonoverlapping populations (Sato and Svoboda, 2010; Chen et al., 2013; Yamashita et al., 2013) with different gene-expression profiles (Sorensen et al., 2015), different intrinsic membrane properties, and different signatures of sensory-evoked postsynaptic potentials (PSPs) (Yamashita et al., 2013). Specifically, S2-p neurons receive slow, small, and less depressing PSPs that can be summated during repetitive touch, allowing sustained signaling, whereas M1-p neurons receive fast, large and strongly depressing PSPs, giving only transient signaling (Yamashita et al., 2013).

Interestingly, associating a whisker stimulus with a reward causes signals conveyed by S2-p and M1-p neurons to be further tuned (Chen et al., 2013, 2015a; Kwon et al., 2016; Yamashita and Petersen, 2016): Learning of an S1-dependent whisker deflection

detection task (Sachidhanandam et al., 2013) induces choice-related depolarization and firing in S2-p neurons, but not in M1-p neurons (Yamashita and Petersen, 2016). Therefore, processing of synaptic input by distinct projection neurons controls large-scale routing of sensory information dynamically in mouse sensorimotor cortex.

Although, so far, work in somatosensory cortex has mostly defined active behavior based on the animal's whisking, some recent studies have begun to investigate somatosensory processing during locomotion (Fu et al., 2014; Pluta et al., 2015; Sofroniew et al., 2015; Ayaz et al., 2016).

Visual cortex

Porting the method of fixating animals on air-cushioned balls from flies to rodents (Hölscher et al., 2005; Dombek et al., 2007) allowed for remarkable progress on the signatures and neural circuits underlying state-dependent processing based on locomotor activity in the visual cortex (Niell and Stryker, 2010). In addition, inspired by attention research in humans (Bradshaw, 1967), several groups have recently started to read out changes in behavioral state also from the mouse's pupil, even in periods when the animal is stationary (Reimer et al., 2014; McGinley et al., 2015a; Vinck et al., 2015).

In the visual system, locomotion- or pupil-indexed increases in arousal predispose the cortex toward robust visual encoding by enhancing spiking responses (Niell and Stryker, 2010; Bennett et al., 2013; Polack et al., 2013; Eriskin et al., 2014; Lee et al., 2014; Reimer et al., 2014; Vinck et al., 2015) in both multiplicative and additive ways (Mineault et al., 2016; Dadarlat and Stryker, 2017), and by generating gamma-band oscillations in the local field potentials (Lee et al., 2014; Saleem et al., 2017; Storchi et al., 2017). The response enhancements were first observed during measurements of orientation-tuning of neurons in L2/3 of primary visual cortex (V1), where median responses to optimal orientations can be >2-fold higher during locomotion than stationary periods without consistent changes in tuning width (Niell and Stryker, 2010). These V1-state-dependent modulations of gain seem to be mediated, as in somatosensory cortex, by a locomotion-related depolarization of the membrane potential and a decrease in its variance (Bennett et al., 2013; Polack et al., 2013). Although increased visual responses can be observed across all V1 layers, gain modulation seems to be strongest and most consistent in L2/3 (Eriskin et al., 2014; Dadarlat and Stryker, 2017).

In addition to regulating response gain, locomotion and arousal also modulate the selectivity of visual responses. First, locomotion can control visual spatial integration (Ayaz et al., 2013; Eriskin et al., 2014) by reducing surround suppression and shifting the neurons' preference toward larger stimulus sizes. Second, locomotion-related gain changes are particularly pronounced in neurons preferring high spatial frequencies, leading to increased spatial resolution during locomotion (Mineault et al., 2016). Third, in V1 and extrastriate areas, locomotion increases peak speed by shifting temporal frequency tuning to higher values (Andermann et al., 2011). Fourth, in periods of high arousal, as indexed by pupil dilation, but in the absence of running, saccadic eye movements, or whisking, orientation tuning is sharpened (Reimer et al., 2014).

Importantly, periods of high arousal and motor activity are also associated with decreased response variability. Locomotion decreases trial-by-trial response variability of V1 subthreshold membrane potentials (Bennett et al., 2013) and both locomotion and arousal without locomotion decrease noise correlations in the population (Eriskin et al., 2014; Vinck et al., 2015; Dadarlat

and Stryker, 2017). Together with the locomotion-related enhanced visual responses (Niell and Stryker, 2010; Eriskin et al., 2014; Lee et al., 2014; Reimer et al., 2014; Vinck et al., 2015), this likely contributes to the enhanced mutual information between visual stimuli and V1 single neuron responses during locomotion (Dadarlat and Stryker, 2017).

In addition to state-dependent modulation by arousal and locomotion, neural representations in primary visual cortex can be further shaped by more specific behaviors, such as focusing attention (Roelfsema et al., 1998), timing of signals (Shuler and Bear, 2006), anticipation of rewards (Poort et al., 2015), and learning (Poort et al., 2015; Jurjut et al., 2017). Recent work suggests that these active processes, which may include feedback projections providing top-down motor-related information or task-specific regulation of targeted excitatory and inhibitory neurons (Zhang et al., 2014; Vinck et al., 2015; Garcia-Junco-Clemente et al., 2017), may regulate arousal-dependent visual processing transiently (discussed further in the "Circuit-level mechanisms underlying action-dependent changes of neural processing" section).

Auditory cortex

In contrast to the overall enhancement of neural responses observed in somatosensory and visual cortex, locomotion-indexed active states are associated with a suppression of L2/3 excitatory neuron spiking responses in primary auditory cortex (A1) (Zhou et al., 2014; Schneider et al., 2014), mediated by a scaling down of both excitatory and inhibitory synaptic inputs (Zhou et al., 2014). Such suppression of sound responses is also observed during engagement in more complex auditory tasks (Otazu et al., 2009; Kuchibhotla et al., 2017). In addition to the sign of modulation in auditory cortex being opposite to that observed in visual cortex, the signal-to-noise ratio is also degraded (Zhou et al., 2014; McGinley et al., 2015a), perhaps suggesting that the auditory system in rodents is most effectively engaged during stillness.

Recent work has used pupil-indexed behavioral state to track rapid changes of auditory cortex sound responses and performance in auditory behavioral tasks (McGinley et al., 2015a). When the pupil was small, layer 5 auditory cortical neurons were engaged in slow (2–10 Hz) oscillations, membrane potential responses and spiking responses to sounds were small and unreliable, and behavioral performance was poor. In this state, sharp waves were prominent in the hippocampus, suggesting that "drowsiness" associated with a constricted pupil was global across the brain. At mid-sized pupil diameters, auditory cortical neurons were in a tonically hyperpolarized state, sound responses were large and reliable, and behavioral performance was optimal. During sustained large pupil diameters (usually associated with walking), neurons were tonically depolarized and sound responses and behavioral performance were again degraded. Therefore, optimal behavior and cortical processing of sounds occurs in a substate of stillness, suggesting the need to parse brain and behavioral states more finely than into stillness versus locomoting.

Active behaviors modulate neural processing in the thalamus

Modulations of neural responses by behavior are not restricted to cortex, but already occur at the level of the thalamus. In fact, beyond its classical role in relaying information to or between cortical regions (Sherman and Guillery, 2001), the thalamus is ideally suited via its extensive reciprocal cortical connections through structurally diverse circuit motifs (Clascá et al., 2012) to gate and modulate information processing and to control remapping of cortical RF properties (Nakajima and Halassa, 2017). Most thalamic nuclei receive putative driving inputs from the

cortex rather than the periphery, particularly in primates (Rovó et al., 2012). Intriguingly, these cortical inputs exhibit a high degree of convergence in regions such as the pulvinar and the mediodorsal thalamus (MD) (Rovó et al., 2012) and, across the thalamus, principal neurons can exhibit a variety of structural output patterns, with individual MD or pulvinar neurons, for example, covering several millimeters of cortical space (Rockland, 2002; Kuramoto et al., 2017). Because sensory RFs in these nuclei may either be large in space or ill defined, their sensory representations are unlikely to be the proximal cause for cortical sensory RFs.

Instead, multiple recent lines of evidence call for an expanded view of the thalamus in cortical function and cognition. First, beyond fundamental, well described state-dependent differences in thalamic firing mode (for review, see McCormick and Bal, 1997), the activity of thalamic neurons signals diverse contextual information. In the visual system, both the dorsolateral geniculate nucleus (dLGN; Erisken et al., 2014; Williamson et al., 2015; Roth et al., 2016) and the lateral posterior nucleus (LP, the rodent homolog of the pulvinar; Roth et al., 2016) carry locomotion signals. For the dLGN, these locomotion signals seem to represent a combination of visual and running speed; for LP, these signals indicate discrepancies between visual and self-motion (Roth et al., 2016). Modulations of neural responses with pupil size were also observed in auditory thalamus in the medial geniculate (MG) body, particularly in association with walking (McCormick et al., 2015; McGinley et al., 2015a; Williamson et al., 2015; but see Zhou et al., 2014). In the auditory system, proprioceptive input associated with walking may already suppress sound responses in the inferior colliculus (Aitkin et al., 1978; McGinley and McCormick, unpublished data) and locomotion effects in auditory cortex may additionally result from top-down corollary discharge influences (Schneider et al., 2014).

Second, a novel, currently emerging view is that the thalamus affects the “computational state” of the cortex by controlling functional connections within and across cortical areas (Nakajima and Halassa, 2017). This novel thalamic function would enable remapping cortical RFs in a task-dependent manner. In fact, rather than relaying task-category-specific signals themselves, certain circuits within the MD and pulvinar have been shown to control effective connectivity within and/or across task-relevant areas that they innervate (Schmitt et al., 2017). In a task in which mice maintained abstract rules in mind over a delay, Schmitt et al. (2017) found evidence that task rules were encoded by specific PFC neuronal subpopulations via spike timing relationships normally associated with direct synaptic transmission, that is, via local recurrence. Although MD of the thalamus lacked task-specific local recurrence, optogenetic suppression of MD diminished PFC rule representation and the ability of the mouse to select its target appropriately. Enhancing MD spiking, in turn, enhanced local PFC recurrence and behavioral performance. Collectively, these experiments indicate that MD spiking cannot be the proximal cause of PFC RFs in this task, but instead MD spikes fulfill the computational role of shifting PFC RFs to a mode in which the relevant inputs are those of their neighbors. A similar function may explain the finding that neurons within the inferior pulvinar reflect decision confidence rather than category in a dot motion task (Komura et al., 2013), in contrast to what their targets in parietal cortex are known to reflect (Kiani and Shadlen, 2009). Overall, the idea that the thalamus encodes contextual signals to remap cortical RFs in a task-relevant manner provides a unique mechanism for cognitive flexibility. Testing this idea across different circuits and models will provide impor-

tant insights into the general role of the thalamus in cognitive function.

Circuit-level mechanisms underlying action-dependent changes of neural processing

The immense adaptivity of cortical circuits on fast timescales is likely controlled by a combination of circuit-level mechanisms that are beginning to be unraveled. One key mediator of brain state is neuromodulation, which can regulate thalamocortical circuits (McCormick and Prince, 1986; McCormick, 1989; Steriade, 2004) and exert influence directly within the cortex (Newman and Symmes, 1974; Manunta and Edeline, 1999). Neuromodulatory inputs to cortex may act on multiple targets, including thalamocortical terminals (Kruglikov and Rudy, 2008), pyramidal neurons (McCormick and Prince, 1986; Disney et al., 2007; Gullledge et al., 2007, 2009), and diverse GABAergic interneurons (Kawaguchi, 1997; Porter et al., 1999; Fanselow et al., 2008; Alitto and Dan, 2012; Chen et al., 2015b; Batista-Brito et al., 2017; Muñoz et al., 2017).

One of the most striking examples of the impact of neuromodulation is the dramatic shift observed in frequency tuning of auditory cortex neurons during associative learning (Bakin and Weinberger, 1990; Recanzone et al., 1993; Fritz et al., 2003; David et al., 2012). These shifts seem to be critically related to the appropriately timed release of acetylcholine (Metherate and Weinberger, 1989; Kilgard and Merzenich, 1998; Thiel et al., 2002; Froemke et al., 2007) and norepinephrine (Manunta and Edeline, 1999; Martins and Froemke, 2015). More generally, the regulation of auditory cortical responses during task engagement seem to result in part from neuromodulation (Otazu et al., 2009; Kuchibhotla et al., 2017).

Not surprisingly, acetylcholine and norepinephrine are also two of the key neuromodulatory systems involved in modulations of sensory processing across sensory systems during locomotion- and pupil-indexed behaviors. GCaMP activity of cholinergic projections measured at the V1 and A1 surface seems coherent with locomotor activity and the associated slower changes in pupil size (Reimer et al., 2016). Accordingly, stimulation of cholinergic neurons in basal forebrain (Pinto et al., 2013) or afferent projections from the midbrain locomotor region to the basal forebrain (Lee et al., 2014) is sufficient to mimic some of the neural signatures of locomotion in area V1. GCaMP activity of noradrenergic projections to V1, in turn, is correlated with rapid changes in pupil diameter (Reimer et al., 2014) and application of noradrenergic receptor antagonists in V1 can markedly reduce locomotion-dependent membrane depolarization (Polack et al., 2013). Other neuromodulatory systems, including serotonin (5-HT) (Matias et al., 2017), are also likely to play key roles in shaping cortical circuits “online” during behavior.

Neuromodulation during active behavior, potentially interacting with top-down excitatory feedback projections (Zhang et al., 2014), might affect GABAergic interneurons preferentially. Differential recruitment of GABAergic interneurons into the ongoing pattern of activity, in turn, may change the functional cortical circuit (Fu et al., 2014; Pakan et al., 2016; see also Dipoppa et al., 2016) and thereby shift the cortex from one processing mode to another on a moment-to-moment basis during wakefulness. A mechanism for circuit selection during behavior that has received particular attention is the state-dependent cholinergic modulation of the activity of vasoactive intestinal peptide (VIP)- and somatostatin (SST)-expressing GABAergic interneurons (Fu et al., 2014; Reimer et al., 2014; Pakan et al., 2016). VIP interneurons express 5-HT_{3a} and nACh receptors, are innervated by serotonergic and cholinergic afferents (Lee et al., 2010, 2013; Fu et

al., 2014; Kamigaki and Dan, 2017), and are activated by both glutamatergic and neuromodulatory inputs (Porter et al., 1999; Prönneke et al., 2015; Batista-Brito et al., 2017; Kuchibhotla et al., 2017). VIP interneurons can regulate cortical excitatory activity and sensory response gain (Lee et al., 2013; Pi et al., 2013; Fu et al., 2014; Garcia-Junco-Clemente et al., 2017) through their preferential inhibition of SST interneurons (Pfeffer et al., 2013) and consequent disinhibition of pyramidal cells. SST interneurons themselves are also strongly regulated by cholinergic inputs via muscarinic ACh receptors (Fanselow et al., 2008; Chen et al., 2015b) and PV interneurons may likewise be controlled by acetylcholine release (Yi et al., 2014; Kuchibhotla et al., 2017). Cortical representations of sensory information may thus be regulated by state-dependent neuromodulatory sculpting of GABAergic participation in the local circuit. Although disinhibition of pyramidal neurons via cholinergic engagement of VIP interneurons is likely too simplistic a model to fully capture the dynamics of state-dependent cortical activity (Pakan et al., 2016), the rules by which neuromodulators control and modify sensory processing and perception are beginning to emerge.

Functions for action-dependent modulations in sensory coding

As we have discussed throughout this review, neural populations in sensory areas show diverse changes in their responses during active behaviors, but what is the function of such changes? As predicted by previous studies (Niell and Stryker, 2010; Reimer et al., 2014; Vinck et al., 2015), the enhanced cortical signal-to-noise ratio to sensory inputs during active states is translated into decreases in the perceptual threshold for visual (Bennett et al., 2013) and auditory (McGinley et al., 2015a) detection.

Most studies access activity level as a binary state and compare sensory processing between inactive and active states. The active state, however, is likely multileveled depending on the degree of activity or engagement (McGinley et al., 2015b). This would be particularly relevant when an animal is using the sensory information toward an active process. A few examples of such active processes are feedback control, object detection, and navigation. In feedback control, the animal can use sensory information to control its speed of movement. Consistent with this, 5–10% of neurons in mouse V1 have been found to represent a sudden perturbation of visual flow in conflict with the animal's own movements (Keller et al., 2012; Zmarz and Keller, 2016). In addition, ~5% of V1 neurons may respond selectively to perturbations of local optic flow (Zmarz and Keller, 2016), a signal that may enhance detection of objects moving independently from the animal.

The visual system can aid navigation in two ways: to track the distance that an animal has moved through the environment and to identify landmarks. To track distance, one would have to maintain an estimate of one's self-motion. Traditionally, the primary visual cortex was assumed to do this using only visual flow. However, the running speed of the animal is represented in mouse V1 even in the absence of any visual flow. Specifically, in darkness, neurons have a varied representation of running speed, from monotonically increasing or decreasing with speed, to being tuned to specific speeds (Saleem et al., 2013). This running speed information is then integrated with the speed detected based on visual motion (Saleem et al., 2013), consistent with the possibility that the speed encoded by a primary sensory area can inform navigation. Running-speed-dependent activity has also been found in visual thalamic nuclei dLGN and LP (Erisken et al., 2014; Roth et al., 2016) and the somatosensory cortex (Sofroniew et al., 2015).

There is also growing evidence for encoding of visual landmarks of the environment in primary visual cortex, where activity is not just controlled by the visual stimuli hitting the retina, but can also be modulated by the spatial context or position of the animal in the environment (Fiser et al., 2016; Saleem et al., 2016; Diamanti et al., 2017; Fournier et al., 2017), and the behavior of the animal (Saleem et al., 2016). First, identical visual stimuli presented in different positions of the environment elicit different responses in individual neurons of the primary visual cortex (Saleem et al., 2016; Diamanti et al., 2017). This spatial-context-dependent modulation is further enhanced in higher visual areas of the mouse brain (Diamanti et al., 2017). When an animal is engaged in a navigational task, behavioral errors are correlated with the errors in decoding the animal's position from the visual cortex (Saleem et al., 2016). Therefore, the primary visual cortex also holds correlates of the animal's behavior.

Future perspectives

In the last few years, there has been a growing understanding of how sensory processing is modulated during active behaviors. This has unraveled a whole new area of research with many open questions and challenges, some of which we list below.

1. Mechanisms underlying action-dependent modulation

Despite substantial progress, our knowledge about the mechanisms and circuits mediating activity-dependent modulation of sensory processing remains rather coarse. Even within genetically defined populations, behavior-dependent effects typically show considerable variability and a broad distribution, but only a few studies to date have succeeded in explaining some of this variability by further subdividing the populations using additional markers such as projection targets or laminar location (Yamashita et al., 2013; Erisken et al., 2014; Ayaz et al., 2016; Yamashita and Petersen, 2016; Muñoz et al., 2017). The rapidly growing arsenal of transgenic animals and viral tools for intersectional targeting will allow refined investigations and more specific insights.

2. Cascade effects

As reviewed here, active behaviors affect sensory areas at different levels. Modulations of thalamic processing can cascade to the cortex or modulations of cortical processing can be carried over from one cortical region to another via glutamatergic projections. Therefore, such cascade effects likely also contribute to setting the brain's processing regime, potentially in a fast and spatially precise way (for review, see Zgha and McCormick, 2014). Some open questions include: How does a downstream area deal with such changing input? And to which degree are effects of behavioral state or modulations by more complex behaviors "reinvented" across multiple processing stages or inherited?

3. Sensation during unrestrained movements

Most of the results that we have discussed have been performed in head-restrained animals walking/running on treadmills. The key limitation has been the inability to present controlled sensory stimuli in unrestrained animals. Recent years have seen important technological developments including eye tracking in freely moving rats (Wallace et al., 2013) and virtual reality systems with animal tracking and low-latency large-scale projections (Del Grosso et al., 2017; Stowers et al., 2017). These developments can help improve our ability to present controlled stimuli, and thus a systematic analysis of sensory processing, in unrestrained animals.

4. Behavioral-task-dependent processing

Spontaneous and natural behaviors such as whisking and locomotion have been a valuable tool in uncovering state-dependent interactions in brain circuits of awake, behaving mice. However, small, uncontrolled differences in environmental context, behavioral state, stress or anxiety levels, and sensory stimulation across studies may present challenges for understanding the detailed relationship between behavioral state and processing. A higher degree of experimental control and exquisite access to more complex behavioral repertoires can be achieved by approaches in which animals are trained over several weeks (Histed et al., 2012; Glickfeld et al., 2013; Poort et al., 2015; Wimmer et al., 2015; Burgess et al., 2017; Montijn et al., 2016; Takahashi et al., 2016; Jurjut et al., 2017; Schmitt et al., 2017). Increasingly, efforts are being made to consider the natural habitat of animals and the evolutionary relevance of behaviors in the study of behavioral-task-dependent processing (De Franceschi et al., 2016; Hoy et al., 2016).

5. Naturalistic and complex behaviors

Natural behaviors are highly variable, context dependent, and erratic. Here, traditional concepts such as repeated presentations of an identical stimulus across trials become obsolete. Promising technological developments have been made in terms of high-dimensional data approaches such as detailed animal tracking and automatic segmentation of behavioral states, which help us delve into high-dimensional and complex naturalistic behaviors. The future challenge will be to incorporate the analyses of such spontaneous, high-dimensional, complex natural behaviors with more abstract concepts of the behavior, including its functional and evolutionary role (Krakauer et al., 2017).

6. Are modulations species dependent?

Until now, different types of behavior-dependent modulations of neural processing have been mostly investigated in different species: the circuit-level work on effects of locomotion has been performed mostly in insects and rodents; questions of attentional modulation of neural responses have been investigated mostly in primates; and perceptual changes during locomotion have been addressed in human psychophysics (Pelah and Barlow, 1996; Prokop et al., 1997; Warren et al., 2001). It is therefore unclear whether the observed behavior-dependent effects are universal to all species. Alternately, the extrasensory influences on sensory processing could be more prominent in the mouse, potentially reflecting the flatter cortical hierarchy in mice compared with monkeys or other evolutionary differences. More generally, extrasensory influences could vary from species to species, reflecting the ethological demands that are unique to each.

“The simple assumption that the perception of the world is caused by stimuli from the world will not do” . . . “we look around, walk up to something interesting and move around it so as to see it from all sides, and go from one vista to another. That is natural vision” –J.J. Gibson, 1904–1979.

We have known for many years that studying sensation during natural active behaviors is important, but we have not been in the position to investigate it. Equipped with new techniques and better background, we are at an exciting juncture to address many unresolved questions.

References

- Aitkin LM, Dickhaus H, Schult W, Zimmermann M (1978) External nucleus of inferior colliculus: auditory and spinal somatosensory afferents and their interactions. *J Neurophysiol* 41:837–847. [Medline](#)

- Alitto HJ, Dan Y (2012) Cell-type-specific modulation of neocortical activity by basal forebrain input. *Front Syst Neurosci* 6:79. [CrossRef Medline](#)
- Andermann ML, Kerlin AM, Roumis DK, Glickfeld LL, Reid RC (2011) Functional specialization of mouse higher visual cortical areas. *Neuron* 72:1025–1039. [CrossRef Medline](#)
- Aronoff R, Matyas F, Mateo C, Ciron C, Schneider B, Petersen CC (2010) Long-range connectivity of mouse primary somatosensory barrel cortex. *Eur J Neurosci* 31:2221–2233. [CrossRef Medline](#)
- Ayaz A, Saleem AB, Schölvinck ML, Carandini M (2013) Locomotion controls spatial integration in mouse visual cortex. *Curr Biol* 23:890–894. [CrossRef Medline](#)
- Ayaz A, Stauble A, Helmchen F (2016) Layer-specific somatosensory processing in head-restrained mice during exploratory locomotion. Program No. 149.10. 2016 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience.
- Azañón E, Longo MR, Soto-Faraco S, Haggard P (2010) The posterior parietal cortex remaps touch into external space. *Curr Biol* 20:1304–1309. [CrossRef Medline](#)
- Bakin JS, Weinberger NM (1990) Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. *Brain Res* 536:271–286. [CrossRef Medline](#)
- Batista-Brito R, Vinck M, Ferguson KA, Chang JT, Laubender D, Lur G, Mossner JM, Hernandez VG, Ramakrishnan C, Deisseroth K, Higley MJ, Cardin JA (2017) Developmental dysfunction of VIP interneurons impairs cortical circuits. *Neuron* 95:884–895.e9. [CrossRef Medline](#)
- Bennett C, Arroyo S, Hestrin S (2013) Subthreshold mechanisms underlying state-dependent modulation of visual responses. *Neuron* 80:350–357. [CrossRef Medline](#)
- Borst A (2014) Fly visual course control: behaviour, algorithms and circuits. *Nat Rev Neurosci* 15:590–599. [CrossRef Medline](#)
- Bradshaw J (1967) Pupil size as a measure of arousal during information processing. *Nature* 216:515–516. [CrossRef Medline](#)
- Buchner E (1976) Elementary movement detectors in an insect visual system. *Biol Cybern* 24:85–101. [CrossRef](#)
- Burgess CP, Lak A, Steinmetz N, Zátka-Haas P, Reddy CB, Jacobs EAK, Linden JF, Paton JJ, Ranson A, Schroeder S, Soares S, Wells MJ, Wool LE, Harris KD, Carandini M (2017) High-yield methods for accurate two-alternative visual psychophysics in head-fixed mice. *Cell Rep* 2017;20:2513–2524. [CrossRef](#)
- Chapman JW, Klaassen RH, Drake VA, Fossette S, Hays GC, Metcalfe JD, Reynolds AM, Reynolds DR, Alerstam T (2011) Animal orientation strategies for movement in flows. *Curr Biol* 21:R861–R870. [CrossRef Medline](#)
- Chen JL, Carta S, Soldado-Magraner J, Schneider BL, Helmchen F (2013) Behaviour-dependent recruitment of long-range projection neurons in somatosensory cortex. *Nature* 499:336–340. [CrossRef Medline](#)
- Chen JL, Margolis DJ, Stankov A, Sumanovski LT, Schneider BL, Helmchen F (2015a) Pathway-specific reorganization of projection neurons in somatosensory cortex during learning. *Nat Neurosci* 18:1101–1108. [CrossRef Medline](#)
- Chen N, Sugihara H, Sur M (2015b) An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity. *Nat Neurosci* 18:892–902. [CrossRef Medline](#)
- Chiappe ME, Seelig JD, Reiser MB, Jayaraman V (2010) Walking modulates speed sensitivity in *Drosophila* motion vision. *Curr Biol* 20:1470–1475. [CrossRef Medline](#)
- Clascá F, Rubio-Garrido P, Jabaudon D (2012) Unveiling the diversity of thalamocortical neuron subtypes. *Eur J Neurosci* 35:1524–1532. [CrossRef Medline](#)
- Crochet S, Petersen CC (2006) Correlating whisker behavior with membrane potential in barrel cortex of awake mice. *Nat Neurosci* 9:608–610. [CrossRef Medline](#)
- Crochet S, Poulet JF, Kremer Y, Petersen CC (2011) Synaptic mechanisms underlying sparse coding of active touch. *Neuron* 69:1160–1175. [CrossRef Medline](#)
- Dadarlat MC, Stryker MP (2017) Locomotion enhances neural encoding of visual stimuli in mouse V1. *J Neurosci* 37:3764–3775. [CrossRef Medline](#)
- David SV, Fritz JB, Shamma SA (2012) Task reward structure shapes rapid receptive field plasticity in auditory cortex. *Proc Natl Acad Sci U S A* 109:2144–2149. [CrossRef Medline](#)
- De Franceschi G, Vivattanasarn T, Saleem AB, Solomon SG (2016) Vision guides selection of freeze or flight defense strategies in mice. *Curr Biol* 26:2150–2154. [CrossRef Medline](#)

- Del Grosso NA, Graboski JJ, Chen W, Hernández EB, Sirota A (2017) Virtual reality system for freely-moving rodents. *bioRxiv*:161232.
- Diamanti D, Saleem AB, Fournier J, Harris KD, Carandini M (2017) Mapping navigation-related signals in mouse visual areas. Program No. 147.07. 2017 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience.
- Dipoppa M, Ranson A, Krumin M, Pachitariu M, Carandini M, Harris KD (2016) Vision and locomotion shape the interactions between neuron types in mouse visual cortex. *bioRxiv*:58396.
- Disney AA, Aoki C, Hawken MJ (2007) Gain modulation by nicotine in macaque v1. *Neuron* 56:701–713. [CrossRef Medline](#)
- Dombeck DA, Khabbazi AN, Collman F, Adelman TL, Tank DW (2007) Imaging large-scale neural activity with cellular resolution in awake, mobile mice. *Neuron* 56:43–57. [CrossRef Medline](#)
- Erisken S, Vaiceliunaite A, Jurjut O, Fiorini M, Katzner S, Busse L (2014) Effects of locomotion extend throughout the mouse early visual system. *Curr Biol* 24:2899–2907. [CrossRef Medline](#)
- Fanselow EE, Richardson KA, Connors BW (2008) Selective, state-dependent activation of somatostatin-expressing inhibitory interneurons in mouse neocortex. *J Neurophysiol* 100:2640–2652. [CrossRef Medline](#)
- Fiser A, Mahringer D, Oyibo HK, Petersen AV, Leinweber M, Keller GB (2016) Experience-dependent spatial expectations in mouse visual cortex. *Nat Neurosci* 19:1658–1664. [CrossRef Medline](#)
- Fournier J, Saleem AB, Wells M, Harris KD, Carandini M (2017) Simultaneous spatial representations in visual cortex and hippocampus. Program No. 147.06. 2017 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience.
- Fritz J, Shamma S, Elhilali M, Klein D (2003) Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex. *Nat Neurosci* 6:1216–1223. [CrossRef Medline](#)
- Froemke RC, Merzenich MM, Schreiner CE (2007) A synaptic memory trace for cortical receptive field plasticity. *Nature* 450:425–429. [CrossRef Medline](#)
- Fu Y, Tucciarone JM, Espinosa JS, Sheng N, Darcy DP, Nicoll RA, Huang ZJ, Stryker MP (2014) A cortical circuit for gain control by behavioral state. *Cell* 156:1139–1152. [CrossRef Medline](#)
- Fujiwara T, Cruz TL, Bohoslav JP, Chiappe ME (2017) A faithful internal representation of walking movements in the *Drosophila* visual system. *Nat Neurosci* 20:72–81. [CrossRef Medline](#)
- Garcia-Junco-Clemente P, Ikrar T, Tring E, Xu X, Ringach DL, Trachtenberg JT (2017) An inhibitory pull-push circuit in frontal cortex. *Nat Neurosci* 20:389–392. [CrossRef Medline](#)
- Gentet LJ, Avermann M, Matyas F, Staiger JF, Petersen CC (2010) Membrane potential dynamics of GABAergic neurons in the barrel cortex of behaving mice. *Neuron* 65:422–435. [CrossRef Medline](#)
- Glickfeld LL, Histed MH, Maunsell JH (2013) Mouse primary visual cortex is used to detect both orientation and contrast changes. *J Neurosci* 33:19416–19422. [CrossRef Medline](#)
- Gu Y, Angelaki DE, Deangelis GC (2008) Neural correlates of multisensory cue integration in macaque MSTd. *Nat Neurosci* 11:1201–1210. [CrossRef Medline](#)
- Gulledge AT, Park SB, Kawaguchi Y, Stuart GJ (2007) Heterogeneity of phasic cholinergic signaling in neocortical neurons. *J Neurophysiol* 97:2215–2229. [CrossRef Medline](#)
- Gulledge AT, Bucci DJ, Zhang SS, Matsui M, Yeh HH (2009) M1 receptors mediate cholinergic modulation of excitability in neocortical pyramidal neurons. *J Neurosci* 29:9888–9902. [CrossRef Medline](#)
- Hall NJ, Colby CL (2011) Remapping for visual stability. *Philos Trans R Soc Lond B Biol Sci* 366:528–539. [CrossRef Medline](#)
- Harris KD, Thiele A (2011) Cortical state and attention. *Nat Rev Neurosci* 12:509–523. [CrossRef Medline](#)
- Hausen K (1982) Motion sensitive interneurons in the optomotor system of the fly. *Biol Cybern* 46:67–79. [CrossRef](#)
- Hausen K, Wehrhahn C (1990) Neural circuits mediating visual flight control in flies. II. Separation of two control systems by microsurgical brain lesions. *J Neurosci* 10:351–360. [Medline](#)
- Histed MH, Carvalho LA, Maunsell JH (2012) Psychophysical measurement of contrast sensitivity in the behaving mouse. *J Neurophysiol* 107:758–765. [CrossRef Medline](#)
- Hölscher C, Schnee A, Dahmen H, Setia L, Mallot HA (2005) Rats are able to navigate in virtual environments. *J Exp Biol* 208:561–569. [CrossRef Medline](#)
- Hoy JL, Yavorska I, Wehr M, Niell CM (2016) Vision drives accurate approach behavior during prey capture in laboratory mice. *Curr Biol* 26:3046–3052. [CrossRef Medline](#)
- Hubel DH (1959) Single unit activity in striate cortex of unrestrained cats. *J Physiol* 147:226–238. [CrossRef Medline](#)
- Hubel DH (1982) Evolution of ideas on the primary visual cortex, 1955–1978: a biased historical account. *Biosci Rep* 2:435–469. [CrossRef Medline](#)
- Hubel DH, Wiesel TN (1998) Early exploration of the visual cortex. *Neuron* 20:401–412. [CrossRef Medline](#)
- Joesch M, Plett J, Borst A, Reiff DF (2008) Response properties of motion-sensitive visual interneurons in the lobula plate of *Drosophila melanogaster*. *Curr Biol* 18:368–374. [CrossRef Medline](#)
- Jung SN, Borst A, Haag J (2011) Flight activity alters velocity tuning of fly motion-sensitive neurons. *J Neurosci* 31:9231–9237. [CrossRef Medline](#)
- Jurjut O, Georgieva P, Busse L, Katzner S (2017) Learning enhances sensory processing in mouse V1 before improving behavior. *J Neurosci* 37:6460–6474. [CrossRef Medline](#)
- Kamigaki T, Dan Y (2017) Delay activity of specific prefrontal interneuron subtypes modulates memory-guided behavior. *Nat Neurosci* 20:854–863. [CrossRef Medline](#)
- Kawaguchi Y (1997) Selective cholinergic modulation of cortical GABAergic cell subtypes. *J Neurophysiol* 78:1743–1747. [Medline](#)
- Keller GB, Bonhoeffer T, Hübener M (2012) Sensorimotor mismatch signals in primary visual cortex of the behaving mouse. *Neuron* 74:809–815. [CrossRef Medline](#)
- Kiani R, Shadlen MN (2009) Representation of confidence associated with a decision by neurons in the parietal cortex. *Science* 324:759–764. [CrossRef Medline](#)
- Kilgard MP, Merzenich MM (1998) Cortical map reorganization enabled by nucleus basalis activity. *Science* 279:1714–1718. [CrossRef Medline](#)
- Kim AJ, Fitzgerald JK, Maimon G (2015) Cellular evidence for efference copy in *Drosophila* visuomotor processing. *Nat Neurosci* 18:1247–1255. [CrossRef Medline](#)
- Kim AJ, Fenk LM, Lyu C, Maimon G (2017) Quantitative predictions orchestrate visual signaling in *Drosophila*. *Cell* 168:280–294.e12. [CrossRef Medline](#)
- Komura Y, Nikkuni A, Hirashima N, Uetake T, Miyamoto A (2013) Responses of pulvinar neurons reflect a subject's confidence in visual categorization. *Nat Neurosci* 16:749–755. [CrossRef Medline](#)
- Krakauer JW, Ghazanfar AA, Gomez-Marín A, MacIver MA, Poeppel D (2017) Neuroscience needs behavior: correcting a reductionist bias. *Neuron* 93:480–490. [CrossRef Medline](#)
- Krapp HG, Hengstenberg R, Egelhaaf M (2001) Binocular contributions to optic flow processing in the fly visual system. *J Neurophysiol* 85:724–734. [Medline](#)
- Kruglikov I, Rudy B (2008) Perisomatic GABA release and thalamocortical integration onto neocortical excitatory cells are regulated by neuromodulators. *Neuron* 58:911–924. [CrossRef Medline](#)
- Kuchibhotla KV, Gill JV, Lindsay GW, Papadoyannis ES, Field RE, Sten TA, Miller KD, Froemke RC (2017) Parallel processing by cortical inhibition enables context-dependent behavior. *Nat Neurosci* 20:62–71. [CrossRef Medline](#)
- Kuramoto E, Pan S, Furuta T, Tanaka YR, Iwai H, Yamanaka A, Ohno S, Kaneko T, Goto T, Hioki H (2017) Individual mediodorsal thalamic neurons project to multiple areas of the rat prefrontal cortex: a single neuron-tracing study using virus vectors. *J Comp Neurol* 525:166–185. [CrossRef Medline](#)
- Kwon SE, Yang H, Minamisawa G, O'Connor DH (2016) Sensory and decision-related activity propagate in a cortical feedback loop during touch perception. *Nat Neurosci* 19:1243–1249. [CrossRef Medline](#)
- Lee AM, Hoy JL, Bonci A, Wilbrecht L, Stryker MP, Niell CM (2014) Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. *Neuron* 83:455–466. [CrossRef Medline](#)
- Lee S, Hjerling-Leffler J, Zaghera E, Fishell G, Rudy B (2010) The largest group of superficial neocortical GABAergic interneurons expresses ionotropic serotonin receptors. *J Neurosci* 30:16796–16808. [CrossRef Medline](#)
- Lee S, Kruglikov I, Huang ZJ, Fishell G, Rudy B (2013) A disinhibitory circuit mediates motor integration in the somatosensory cortex. *Nat Neurosci* 16:1662–1670. [CrossRef Medline](#)
- Leutgeb S, Leutgeb JK, Treves A, Moser MB, Moser EI (2004) Distinct ensemble codes in hippocampal areas CA3 and CA1. *Science* 305:1295–1298. [CrossRef Medline](#)
- Longden KD, Muzzu T, Cook DJ, Schultz SR, Krapp HG (2014) Nutritional

- state modulates the neural processing of visual motion. *Curr Biol* 24:890–895. [CrossRef Medline](#)
- Maimon G, Straw AD, Dickinson MH (2010) Active flight increases the gain of visual motion processing in *Drosophila*. *Nat Neurosci* 13:393–399. [CrossRef Medline](#)
- Manunta Y, Edeline JM (1999) Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow-wave sleep. *Eur J Neurosci* 11:2134–2150. [CrossRef Medline](#)
- Martins AR, Froemke RC (2015) Coordinated forms of noradrenergic plasticity in the locus coeruleus and primary auditory cortex. *Nat Neurosci* 18:1483–1492. [CrossRef Medline](#)
- Matias S, Lottem E, Dugué GP, Mainen ZF (2017) Activity patterns of serotonin neurons underlying cognitive flexibility. *Elife* 6: pii: e20552. [CrossRef Medline](#)
- McCormick DA (1989) Cholinergic and noradrenergic modulation of thalamocortical processing. *Trends Neurosci* 12:215–221. [CrossRef Medline](#)
- McCormick DA, Bal T (1997) Sleep and arousal: thalamocortical mechanisms. *Annu Rev Neurosci* 20:185–215. [CrossRef Medline](#)
- McCormick DA, Prince DA (1986) Acetylcholine induces burst firing in thalamic reticular neurons by activating a potassium conductance. *Nature* 319:402–405. [CrossRef Medline](#)
- McCormick DA, McGinley MJ, Salkoff DB (2015) Brain state dependent activity in the cortex and thalamus. *Curr Opin Neurobiol* 31:133–140. [CrossRef Medline](#)
- McGinley MJ, David SV, McCormick DA (2015a) Cortical membrane potential signature of optimal states for sensory signal detection. *Neuron* 87:179–192. [CrossRef Medline](#)
- McGinley MJ, Vinck M, Reimer J, Batista-Brito R, Zagua E, Cadwell CR, Tolias AS, Cardin JA, McCormick DA (2015b) Waking state: rapid variations modulate neural and behavioral responses. *Neuron* 87:1143–1161. [CrossRef Medline](#)
- Metherate R, Weinberger NM (1989) Acetylcholine produces stimulus-specific receptive field alterations in cat auditory cortex. *Brain Res* 480:372–377. [CrossRef Medline](#)
- Mineault PJ, Tring E, Trachtenberg JT, Ringach DL (2016) Enhanced spatial resolution during locomotion and heightened attention in mouse primary visual cortex. *J Neurosci* 36:6382–6392. [CrossRef Medline](#)
- Montijn JS, Olcese U, Pennartz CM (2016) Visual stimulus detection correlates with the consistency of temporal sequences within stereotyped events of V1 neuronal population activity. *J Neurosci* 36:8624–8640. [CrossRef Medline](#)
- Muller RU, Kubie JL (1987) The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J Neurosci* 7:1951–1968. [Medline](#)
- Muñoz W, Tremblay R, Levenstein D, Rudy B (2017) Layer-specific modulation of neocortical dendritic inhibition during active wakefulness. *Science* 355:954–959. [CrossRef Medline](#)
- Nakajima M, Halassa MM (2017) Thalamic control of functional cortical connectivity. *Curr Opin Neurobiol* 44:127–131. [CrossRef Medline](#)
- Newman JD, Symmes D (1974) Arousal effects on unit responsiveness to vocalizations in squirrel monkey auditory cortex. *Brain Res* 78:125–138. [CrossRef Medline](#)
- Niell CM, Stryker MP (2010) Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 65:472–479. [CrossRef Medline](#)
- O'Connor DH, Peron SP, Huber D, Svoboda K (2010) Neural activity in barrel cortex underlying vibrissa-based object localization in mice. *Neuron* 67:1048–1061. [CrossRef Medline](#)
- O'Connor DH, Hires SA, Guo ZV, Li N, Yu J, Sun QQ, Huber D, Svoboda K (2013) Neural coding during active somatosensation revealed using illusory touch. *Nat Neurosci* 16:958–965. [CrossRef Medline](#)
- Otazu GH, Tai LH, Yang Y, Zador AM (2009) Engaging in an auditory task suppresses responses in auditory cortex. *Nat Neurosci* 12:646–654. [CrossRef Medline](#)
- Pakan JM, Lowe SC, Dylida E, Keemink SW, Currie SP, Coutts CA, Rochefort NL (2016) Behavioral-state modulation of inhibition is context-dependent and cell type specific in mouse visual cortex. *Elife* 5: pii: e14985. [CrossRef](#)
- Pelah A, Barlow HB (1996) Visual illusion from running. *Nature* 381:283. [CrossRef Medline](#)
- Peron SP, Freeman J, Iyer V, Guo C, Svoboda K (2015) A cellular resolution map of barrel cortex activity during tactile behavior. *Neuron* 86:783–799. [CrossRef Medline](#)
- Pfeffer CK, Xue M, He M, Huang ZJ, Scanziani M (2013) Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. *Nat Neurosci* 16:1068–1076. [CrossRef Medline](#)
- Pi HJ, Hangya B, Kvitsiani D, Sanders JL, Huang ZJ, Kepecs A (2013) Cortical interneurons that specialize in disinhibitory control. *Nature* 503:521–524. [CrossRef Medline](#)
- Pinto L, Goard MJ, Estandian D, Xu M, Kwan AC, Lee SH, Harrison TC, Feng G, Dan Y (2013) Fast modulation of visual perception by basal forebrain cholinergic neurons. *Nat Neurosci* 16:1857–1863. [CrossRef Medline](#)
- Pluta S, Naka A, Veit J, Telian G, Yao L, Hakim R, Taylor D, Adesnik H (2015) A direct translaminar inhibitory circuit tunes cortical output. *Nat Neurosci* 18:1631–1640. [CrossRef Medline](#)
- Polack PO, Friedman J, Golshani P (2013) Cellular mechanisms of brain state-dependent gain modulation in visual cortex. *Nat Neurosci* 16:1331–1339. [CrossRef Medline](#)
- Poort J, Khan AG, Pachitariu M, Nemri A, Orsolico I, Krupic J, Bauza M, Sahani M, Keller GB, Mrsic-Flogel TD, Hofer SB (2015) Learning enhances sensory and multiple non-sensory representations in primary visual cortex. *Neuron* 86:1478–1490. [CrossRef Medline](#)
- Porter JT, Cauli B, Tsuzuki K, Lambollez B, Rossier J, Audinat E (1999) Selective excitation of subtypes of neocortical interneurons by nicotinic receptors. *J Neurosci* 19:5228–5235. [Medline](#)
- Poulet JF, Petersen CC (2008) Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. *Nature* 454:881–885. [CrossRef Medline](#)
- Prokop T, Schubert M, Berger W (1997) Visual influence on human locomotion: modulation to changes in optic flow. *Exp Brain Res* 114:63–70. [CrossRef Medline](#)
- Prönneke A, Scheuer B, Wagener RJ, Möck M, Witte M, Staiger JF (2015) Characterizing VIP neurons in the barrel cortex of VIPcre/tTomato mice reveals layer-specific differences. *Cereb Cortex* 25:4854–4868. [CrossRef Medline](#)
- Recanzone GH, Schreiner CE, Merzenich MM (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J Neurosci* 13:87–103. [Medline](#)
- Reimer J, Froudarakis E, Cadwell CR, Yatsenko D, Denfield GH, Tolias AS (2014) Pupil fluctuations track fast switching of cortical states during quiet wakefulness. *Neuron* 84:355–362. [CrossRef Medline](#)
- Reimer J, McGinley MJ, Liu Y, Rodenkirch C, Wang Q, McCormick DA, Tolias AS (2016) Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. *Nat Commun* 7:13289. [CrossRef Medline](#)
- Robie AA, Straw AD, Dickinson MH (2010) Object preference by walking fruit flies, *Drosophila melanogaster*, is mediated by vision and graviperception. *J Exp Biol* 213:2494–2506. [CrossRef Medline](#)
- Rockland KS (2002) Visual cortical organization at the single axon level: a beginning. *Neurosci Res* 42:155–166. [CrossRef Medline](#)
- Roelfsema PR, Lamme VA, Spekreijse H (1998) Object-based attention in the primary visual cortex of the macaque monkey. *Nature* 395:376–381. [CrossRef Medline](#)
- Roth MM, Dahmen JC, Muir DR, Imhof F, Martini FJ, Hofer SB (2016) Thalamic nuclei convey diverse contextual information to layer 1 of visual cortex. *Nat Neurosci* 19:299–307. [CrossRef Medline](#)
- Rovó Z, Ulbert I, Acsády L (2012) Drivers of the primate thalamus. *J Neurosci* 32:17894–17908. [CrossRef Medline](#)
- Sachidhanandam S, Sreenivasan V, Kyriakatos A, Kremer Y, Petersen CC (2013) Membrane potential correlates of sensory perception in mouse barrel cortex. *Nat Neurosci* 16:1671–1677. [CrossRef Medline](#)
- Saleem AB, Ayaz A, Jeffery KJ, Harris KD, Carandini M (2013) Integration of visual motion and locomotion in mouse visual cortex. *Nat Neurosci* 16:1864–1869. [CrossRef Medline](#)
- Saleem AB, Fournier J, Harris KD, Carandini (2016) Concordant representation of spatial decisions and uncertain environments in hippocampus and visual cortex. Program No. 554.10. 2016 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience.
- Saleem AB, Lien AD, Krumin M, Haider B, Rosón MR, Ayaz A, Reinhold K, Busse L, Carandini M, Harris KD (2017) Subcortical source and modulation of the narrowband gamma oscillation in mouse visual cortex. *Neuron* 93:315–322. [CrossRef Medline](#)
- Sato TR, Svoboda K (2010) The functional properties of barrel cortex neurons projecting to the primary motor cortex. *J Neurosci* 30:4256–4260. [CrossRef Medline](#)

- Schilstra C, Hateren JH (1999) Blowfly flight and optic flow. I. Thorax kinematics and flight dynamics. *J Exp Biol* 202:1481–1490. [Medline](#)
- Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S, Halassa MM (2017) Thalamic amplification of cortical connectivity sustains attentional control. *Nature* 545:219–223. [CrossRef Medline](#)
- Schneider DM, Nelson A, Mooney R (2014) A synaptic and circuit basis for corollary discharge in the auditory cortex. *Nature* 513:189–194. [CrossRef Medline](#)
- Schnell B, Joesch M, Forstner F, Raghu SV, Otsuna H, Ito K, Borst A, Reiff DF (2010) Processing of horizontal optic flow in three visual interneurons of the *Drosophila* brain. *J Neurophysiol* 103:1646–1657. [CrossRef Medline](#)
- Schnell B, Weir PT, Roth E, Fairhall AL, Dickinson MH (2014) Cellular mechanisms for integral feedback in visually guided behavior. *Proc Natl Acad Sci U S A* 111:5700–5705. [CrossRef Medline](#)
- Sherman SM (2001) Tonic and burst firing: dual modes of thalamocortical relay. *Trends Neurosci* 24:122–126. [CrossRef Medline](#)
- Shuler MG, Bear MF (2006) Reward timing in the primary visual cortex. *Science* 311:1606–1609. [CrossRef Medline](#)
- Silies M, Gohl DM, Clandinin TR (2014) Motion-detecting circuits in flies: coming into view. *Annu Rev Neurosci* 37:307–327. [CrossRef Medline](#)
- Sofroniew NJ, Vlasov YA, Hires SA, Freeman J, Svoboda K (2015) Neural coding in barrel cortex during whisker-guided locomotion. *Elife* 4: pii: e12559. [CrossRef Medline](#)
- Sorensen SA, Bernard A, Menon V, Royall JJ, Glattfelder KJ, Desta T, Hirokawa K, Mortrud M, Miller JA, Zeng H, Hohmann JG, Jones AR, Lein ES (2015) Correlated gene expression and target specificity demonstrate excitatory projection neuron diversity. *Cereb Cortex* 25:433–449. [CrossRef Medline](#)
- Souman JL, Frissen I, Sreenivasa MN, Ernst MO (2009) Walking straight into circles. *Curr Biol* 19:1538–1542. [CrossRef Medline](#)
- Srinivasan M (2001) Visual navigation: the eyes know where their owner is going. *Motion Vision* 181–186.
- Steriade M (2004) Acetylcholine systems and rhythmic activities during the waking–sleep cycle. *Prog Brain Res* 145:179–196. [CrossRef Medline](#)
- Storchi R, Bedford RA, Martial FP, Allen AE, Wynne J, Montemurro MA, Petersen RS, Lucas RJ (2017) Modulation of fast narrowband oscillations in the mouse retina and dLGN according to background light intensity. *Neuron* 93:299–307. [CrossRef Medline](#)
- Stowers JR, Hofbauer M, Bastien R, Griessner J, Higgins P, Farooqui S, Fischer RM, Nowikovsky K, Haubensak W, Couzin ID, Tessmar-Raible K, Straw AD (2017) Virtual reality for freely moving animals. *Nat Methods* 14:995–1002. [CrossRef Medline](#)
- Suver MP, Mamiya A, Dickinson MH (2012) Octopamine neurons mediate flight-induced modulation of visual processing in *Drosophila*. *Curr Biol* 22:2294–2302. [CrossRef Medline](#)
- Takahashi N, Oertner TG, Hegemann P, Larkum ME (2016) Active cortical dendrites modulate perception. *Science* 354:1587–1590. [CrossRef Medline](#)
- Thiel CM, Friston KJ, Dolan RJ (2002) Cholinergic modulation of experience-dependent plasticity in human auditory cortex. *Neuron* 35:567–574. [CrossRef Medline](#)
- Vinck M, Batista-Brito R, Knoblich U, Cardin JA (2015) Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. *Neuron* 86:740–754. [CrossRef Medline](#)
- Wallace DJ, Greenberg DS, Sawinski J, Rulla S, Notaro G, Kerr JN (2013) Rats maintain an overhead binocular field at the expense of constant fusion. *Nature* 498:65–69. [CrossRef Medline](#)
- Warren WH Jr, Kay BA, Zosh WD, Duchon AP, Sahuc S (2001) Optic flow is used to control human walking. *Nat Neurosci* 4:213–216. [CrossRef Medline](#)
- Wiesel TN (1982) The postnatal development of the visual cortex and the influence of environment. *Biosci Rep* 2:351–377. [CrossRef Medline](#)
- Williamson RS, Hancock KE, Shinn-Cunningham BG, Polley DB (2015) Locomotion and task demands differentially modulate thalamic audiovisual processing during active search. *Curr Biol* 25:1885–1891. [CrossRef Medline](#)
- Wimmer RD, Schmitt LI, Davidson TJ, Nakajima M, Deisseroth K, Halassa MM (2015) Thalamic control of sensory selection in divided attention. *Nature* 526:705–709. [CrossRef Medline](#)
- Yamashita T, Petersen CC (2016) Target-specific membrane potential dynamics of neocortical projection neurons during goal-directed behavior. *Elife* 5: pii: e15798. [CrossRef Medline](#)
- Yamashita T, Pala A, Pedrido L, Kremer Y, Welker E, Petersen CC (2013) Membrane potential dynamics of neocortical projection neurons driving target-specific signals. *Neuron* 80:1477–1490. [CrossRef Medline](#)
- Yi F, Ball J, Stoll KE, Satpute VC, Mitchell SM, Pauli JL, Holloway BB, Johnston AD, Nathanson NM, Deisseroth K, Gerber DJ, Tonegawa S, Lawrence JJ (2014) Direct excitation of parvalbumin-positive interneurons by M1 muscarinic acetylcholine receptors: roles in cellular excitability, inhibitory transmission and cognition. *J Physiol* 592:3463–3494. [CrossRef Medline](#)
- Zagha E, McCormick DA (2014) Neural control of brain state. *Curr Opin Neurobiol* 29:178–186. [CrossRef Medline](#)
- Zhang S, Xu M, Kamigaki T, Hoang Do JP, Chang WC, Jenvay S, Miyamichi K, Luo L, Dan Y (2014) Selective attention: long-range and local circuits for top-down modulation of visual cortex processing. *Science* 345:660–665. [CrossRef Medline](#)
- Zhou M, Liang F, Xiong XR, Li L, Li H, Xiao Z, Tao HW, Zhang LI (2014) Scaling down of balanced excitation and inhibition by active behavioral states in auditory cortex. *Nat Neurosci* 17:841–850. [CrossRef Medline](#)
- Zirnsak M, Steinmetz NA, Noudoost B, Xu KZ, Moore T (2014) Visual space is compressed in prefrontal cortex before eye movements. *Nature* 507:504–507. [CrossRef Medline](#)
- Zmarz P, Keller GB (2016) Mismatch receptive fields in mouse visual cortex. *Neuron* 92:766–772. [CrossRef Medline](#)