Perspective
Not so spontaneous: Multi-dimensional representations of behaviors and context in sensory areas
Lilach Avitan1,* and Carsen Stringer2,*
1Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, Jerusalem 9190401, Israel
2HHMI Janelia Research Campus, Ashburn, VA 20147, USA
*Correspondence: lilach.avitan@mail.huji.ac.il (L.A.), stringerc@janelia.hhmi.org (C.S.)
https://doi.org/10.1016/j.neuron.2022.06.019

SUMMARY
Sensory areas are spontaneously active in the absence of sensory stimuli. This spontaneous activity has long been studied; however, its functional role remains largely unknown. Recent advances in technology, allowing large-scale neural recordings in the awake and behaving animal, have transformed our understanding of spontaneous activity. Studies using these recordings have discovered high-dimensional spontaneous activity patterns, correlation between spontaneous activity and behavior, and dissimilarity between spontaneous and sensory-driven activity patterns. These findings are supported by evidence from developing animals, where a transition toward these characteristics is observed as the circuit matures, as well as by evidence from mature animals across species. These newly revealed characteristics call for the formulation of a new role for spontaneous activity in neural sensory computation.

SPONTANEOUS ACTIVITY AND ITS POTENTIAL FUNCTIONAL ROLES
Spontaneous activity (SA) is defined as activity that is not directly driven by external sensory stimuli, i.e., internally generated patterns of neural activity. This activity is observed in many species, from fish to rodents to humans (Fox et al., 2005; Mohajerani et al., 2013; Romano et al., 2015) and in both developing and mature animals. Spontaneous patterns of neural activity are highly structured across neurons and in time (Bartoszek et al., 2021; Clancy et al., 2019; Han et al., 2008; Kenet et al., 2003; Luczak et al., 2009; Miller et al., 2014; see Box 3). These structured neural patterns often also appear during the presentation of sensory stimuli, suggesting that these patterns may interact with sensory processing (Chen et al., 2006). Given the prevalence of SA across sensory areas and species, there exist several hypotheses for its functional role in neural circuits.

Very early in development, SA patterns are hypothesized to aid in circuit development. Indeed, disrupting the structure of early SA alters circuit development (Arroyo and Feller, 2016; Kirkby et al., 2013; Xu et al., 2011), indicating that SA plays a role in the formation of appropriate brain wiring (Ackman and Crair, 2014; Leighton and Lohmann, 2016; Luhmann et al., 2016). However, sensory areas are also spontaneously active after early stages of development when the animal starts interacting with the environment (Avitan et al., 2017; Romano et al., 2015), and key features of SA in developing animals are observed into maturity. Therefore, it is likely that SA serves an additional functional role in more mature animals.

In mature animals, many of the hypothesized roles of SA are based on the characteristics of the recorded activity. For instance, previous studies in passive or anesthetized mice, ferrets, and monkeys found that SA recordings were low dimensional and contained structured synchronous population-wide fluctuations, suggesting that the activity had a limited capacity to store information (Grinvald et al., 2003; Luczak et al., 2009; Okun et al., 2015). Several of these studies also found that the low-dimensional SA patterns were similar to sensory-driven activity (SdA) patterns and that this similarity increased over development (Berkes et al., 2011; Han et al., 2008; Hoffman and McNaughton, 2002; Kenet et al., 2003; Luczak et al., 2009).

Due to the similarity between spontaneous and sensory patterns, the researchers postulated that SA represents prior distributions over stimuli and facilitates Bayesian computations. These studies, however, were limited to quantifying recordings of tens of neurons simultaneously or quantifying neural activity in anesthetized states; it is now possible to monitor hundreds to tens of thousands of neurons in various species while the animals are awake and behaving (Datta et al., 2019; Ji et al., 2016; Vladimirov et al., 2018).

Recent studies using these new recording techniques have reported findings that transform our current understanding of SA. Large-scale recordings across brain areas, species, and developing or mature animals reveal many diverse patterns of neural activity during SA suggestive of high-dimensional structure and thus high capacity to represent various distinct factors, such as various behaviors (Gründemann et al., 2019; Lanore et al., 2021; Pietri et al., 2017; Romano et al., 2015; Stringer et al., 2019b; Strother et al., 2018). Furthermore, these SA patterns are distinct from sensory-driven neural patterns in the visual...
cortex of the awake mouse and in the optic tectum of the awake larval zebrafish (Avitan et al., 2021; Stringer et al., 2019b). This dissimilarity between spontaneous and sensory-driven patterns increases across zebrafish development (Avitan et al., 2021). Other internally generated signals, such as task context and behavioral choice, are also represented by neuronal directions orthogonal to sensory-driven patterns (Goris et al., 2017; Hajnal et al., 2021; Zhao et al., 2020). Together, these studies suggest that sensory areas process information on a background of high-dimensional SA that can represent many variables.

Here, we discuss recent studies describing the properties of SA in both developing and mature animals and across several species. Based on these properties, we propose that SA aids the circuit in combining several internal and external factors to regulate moment-by-moment adaptive behavior. We also examine how the orthogonality of spontaneous and sensory-driven patterns enables faithful representations of external stimuli alongside internal representations.

DEVELOPMENTAL CHANGES IN SPONTANEOUS ACTIVITY INDICATE A NEW FUNCTIONAL ROLE

SA is a hallmark of nervous system development. One of the best-studied drivers for early SA in central visual structures is spontaneous retinal waves which are observed across many species (Ackman and Crair, 2014; Meister et al., 1991; Thompson et al., 2017; Warland et al., 2006; Zhang et al., 2016). These waves drive correlated patterns of activity that propagate across large populations of neurons in visual cortex (Ackman et al., 2012). From a coding perspective, retinal waves provide central structures with sensory statistics similar to those the animal will encounter once its sensory apparatus is better developed (Albert et al., 2008; Butts et al., 2007; Molnár et al., 2020). However, visual cortex is spontaneously active after the disappearance of retinal waves and also active in the mature animal that is capable of executing complex behaviors. How can these patterns contribute to neural sensory processing? To address this question, we will cover recent studies that report the developing features of SA and discuss how these developed features may support the role of SA in sensory computations.

SA in sensory areas of developing animals initially appears as synchronous low-dimensional activity (Figure 1A) (see also Box 1). In the mammalian visual cortex, spontaneous coordinated patterns of neural activity consist of a large fraction of neurons before eye opening (Figure 1Aii), and this fraction progressively increases in the following weeks (Colonnese and Phillips, 2018; Golshani et al., 2009; Rochefort et al., 2009; Siegel et al., 2012). This decorrelation of neurons coincides with a decrease in retinal waves in the second postnatal week (Colonnese and Phillips, 2018; Gribizis et al., 2019; Martini et al., 2021) and allows for intrinsic cortical activity or external drivers to shape SA. High-dimensional intrinsic SA in visual areas was also observed in the developing larval zebrafish even after the removal of the eyes (Avitan et al., 2017; Pietri et al., 2017), in agreement with high-dimensional SA observed in the mammalian mature brain (Figure 1Aii; see section spontaneous activity is high dimensional and Box 3), suggesting that this transition serves a function.

From a coding perspective, the transition to high-dimensional spontaneous neural activity increases the capacity of SA to store distinct factors which may be required during sensory processing.

SA in developing animals continues to reorganize even after the circuit is capable of driving behavior, and these changes are linked to behavior. Evidence linking SA to behavior in developing systems comes from different species. The larval zebrafish visual system is sufficiently mature by 5 days post fertilization for the fish to start hunting for survival (Gahtan et al., 2005). Tectal SA around this day substantially changes with increased overall activity at the single-cell level, increased synchronous activity, and an increase in functional connectivity measures (Avitan et al., 2017). In the functionally mature tectal circuit, SA is organized in several assemblies composed of highly correlated neurons (Avitan et al., 2017; Pietri et al., 2017; Romano et al., 2015; see Box 3). These neuronal assemblies are spatially organized, and their activation predicts orienting tail movements (Pietri et al., 2017; Romano et al., 2015; Figure 1Bi), even in the chronic absence of retinal input (Pietri et al., 2017). In the developing awake rat, an increase in movement-associated firing rates in the visual cortex occurs just before eye opening (between P10 and P13) (Murata and Colonnese, 2018; Figure 1Bi). This link between SA and behavior becomes even stronger in the adult mouse where spontaneous neural activity is predicted with high accuracy from multiple dimensions of facial movements (Figure 1Bii; Benisty et al., 2021; Musall et al., 2019; Salkoff et al., 2020; Stringer et al., 2019b). Thus, SA in developing animals demonstrates an increasing correlation with behavior in agreement with observations in the mammalian adults (see section behavioral representations in spontaneous activity patterns).

Another key feature of the circuit is the relation between sensory-driven and spontaneous patterns of activity over development. Similarity between the two was observed across many species mostly using small-scale recordings in anesthetized animals (Han et al., 2008; Hoffman and McNaughton, 2002; Kenet et al., 2003; Lutzak et al., 2009). This similarity has led to the suggestion that SA maintains an internal model for patterns of activity likely to be evoked by sensory stimuli (Ikezoe et al., 2012; Ringach, 2009) and that during development, SA patterns gradually refine to become more similar to sensory-driven patterns. Although multiunit recordings of spontaneous and sensory-driven activity in 16 neurons showed increasing similarity across development (Berkes et al., 2011), recent work imaging a large population of neurons in the developing optic tectum of the awake larval zebrafish demonstrated that these patterns become less similar and geometrically diverge over development (Avitan et al., 2021; Figure 1C). These sensory-driven patterns of activity were collected in response to prey-like stimuli, which are highly ecologically relevant stimuli for larval survival, and showed a decrease in cosine similarity with spontaneous patterns and a constant degree of overlap in neuron identity members of spontaneous neural assemblies. These findings that the statistics of sensory-driven and SA grow more distant as development proceeds are in agreement with the orthogonality between spontaneous and sensory-driven patterns observed in mature animals (Omer et al., 2019; Stringer et al., 2019b) and suggest that the
A circuit aims for orthogonality and uses it for function (see spontaneous activity is orthogonal to sensory-driven activity). For instance, the circuit can represent many non-sensory factors required for sensory processing in patterns orthogonal to sensory patterns, thus enabling the existence of highly accurate sensory representations alongside non-sensory representations (Poulet and Crochet, 2019; Stringer et al., 2021).

Together, sensory areas process information on a background of SA, which, through development, becomes high dimensional, closely related to behavior, and orthogonal to sensory-driven patterns, i.e., occupying a particular subspace of activity patterns. These key features of SA suggest that in addition to its role in guiding appropriate wiring, SA holds the representation of factors that may be required for processing sensory information and regulating behavior.

**SPONTANEOUS ACTIVITY IS HIGH DIMENSIONAL**
Recent studies in zebrafish, mice, ferrets, monkeys, and humans have revealed that SA contains many diverse neural activity patterns.
patterns (Avitan et al., 2017; Gotts et al., 2020; Lanore et al., 2021; MacDowell and Buschman, 2020; Omer et al., 2019; Smith et al., 2018; Stringer et al., 2019b) (see summary in Table 1). Estimating neural patterns present in SA is not straightforward because there is no trial structure over which to average out single neuron noise like in evoked recordings. Therefore, several recent studies estimate the number of patterns or the dimensionality of spontaneous neural activity in a statistically rigorous way such that only repeatable patterns that spanned many neurons are quantified as significant dimensions (see Box 1; Lanore et al., 2021; MacDowell and Buschman, 2020; Stringer et al., 2019b). Using these techniques, researchers observed that SA in several mouse brain regions is high dimensional. These dimensionality estimates may even be a lower bound of the full circuit dimensionality: the number of dimensions required to explain a certain amount of variance increases with the number of neurons recorded (Lanore et al., 2021; Stringer et al., 2019b).

Previous studies reported low-dimensional SA, suggesting that the number of possible variables represented was limited (Grinvald et al., 2003; Luczak et al., 2009; Okun et al., 2015). However, the dimensionality of SA reported by these studies was likely constrained by the number of neurons recorded or by the state of the animal, e.g., if only 10 neurons are recorded, then the dimensionality of the recording can be at most ten-dimensional (Gao et al., 2017). Another constraint on dimensionality is the complexity of the behavioral task or the external stimuli being presented during the recording (Cowley et al., 2016; Gao et al., 2017): the various neural patterns of SA need to be active during the recording to identify them (see section behavioral representations in spontaneous activity patterns).

Therefore, large-scale recordings in awake and behaving animals, enabled by recent recording techniques, were necessary to reveal the high-dimensional nature of SA.

The existence of many diverse SA patterns in sensory areas suggests that many internal or potentially external variables can be represented. This provides the animal with the ability to keep track of various behavioral and cognitive variables within sensory areas and potentially use these representations in decision-making, rather than combining them in downstream association areas. One advantage of this approach is that precise and high-dimensional sensory information in sensory areas does not need to be conveyed to downstream areas for decision-making, and instead, the filtering of relevant sensory information can be performed directly in the sensory area (Poulet and Crochet, 2019). We will explore the content of SA and its role in computation in the following sections.

**BEHAVIORAL REPRESENTATIONS IN SPONTANEOUS ACTIVITY PATTERNS**

Several SA patterns captured in large-scale recordings correspond to various behaviors such as running, whisking, sniffing, grooming and freezing in mice (Benisty et al., 2021; Clancy et al., 2019; Gründemann et al., 2019; Lanore et al., 2021; Stringer et al., 2019b), leg movements and locomotion in flies (Fujiwara et al., 2017; Strother et al., 2018; Zolin et al., 2021), and tail flicks in zebrafish (Pietri et al., 2017; Romano et al., 2015). Due to the high-dimensional nature of SA, many different behaviors can be represented in the same circuit, and indeed, multiple dimensions of behavior were detected in SA across
ally correlated patterns continue during presentations of sensory stimuli (Stringer et al., 2019b) and during decision-making tasks (Engelhard et al., 2019; Musall et al., 2019; Salkoff et al., 2020; Steinmetz et al., 2019). We explore the cellular mechanisms underlying these behaviorally correlated patterns in Box 2.

Such behavioral representations can interact with incoming sensory signals to modulate overall stimulus responses depending on the behavioral state. For instance, head and body movements modulate visual and auditory stimulus responses in mice, rats, and flies (Bouvier et al., 2020; Chiappe et al., 2010; Dadarlat and Stryker, 2017; Guitchounts et al., 2020; Maimon, 2011; McGinley et al., 2015a; Niell and Stryker, 2010; Vinck et al., 2015; Williamson et al., 2015). These types of movements are often associated with the overall attention or arousal level of the animal, which can be decoded from the pupil diameter (McGinley et al., 2015b). Also, other abstract behavioral states, such as satiation, can alter SA patterns and modulate odor responses in mouse olfactory areas (Allen et al., 2019). This stimulus response modulation observed across various studies is a form of gain modulation that multiplicatively changes all stimulus responses, rather than specifically enhancing the responses to certain stimuli (Ferguson and Cardin, 2020; Figures 2A and 2B). Gain modulation in many cases does not impair linear decoding of sensory stimuli but instead may increase the overall sensory information available in downstream decision-making areas (Abdolrahmani et al., 2021; Allen et al., 2019; Engel et al., 2016; Kanashiro et al., 2017; Ni et al., 2021; Stringer et al., 2021).

Certain behavioral signals have also been shown to modulate specific sensory responses: in flies, courtship behavior was shown to increase the activity of a specific visual pathway for small object detection (Hindmarsh Sten et al., 2021), and in mice, locomotion was shown to increase neural responses to large full-field stimuli relative to responses to smaller stimuli (Ayaz et al., 2013; Busse et al., 2017). Conversely, sensory stimuli can modulate spontaneous, behavior-driven activity: in darkness, head movements decrease neural activity, whereas in light, head movements increase neural activity (Bouvier et al., 2020; Guitchounts et al., 2020). Specific modulation is proposed by the predictive processing hypothesis, which postulates that behavioral signals interact with sensory-driven signals to generate predictions of future stimuli; evidence for this theory exists in visual and auditory areas (Keller and Mrsic-Flogel, 2018). For example, after mice hear the same tone during running for several days, auditory cortical neurons have suppressed responses to the specific running-related tone during running, suggesting the presence of a predictive processing circuit (Schneider et al., 2018). Note that evidence for predictive processing has to be carefully analyzed as both stimulus and motor changes must be controlled for experimentally (see e.g., Muzzo and Saleem, 2021). Also, given the widespread nature of these behavioral representations across brain areas, there are likely additional roles for these signals beyond predictive processing, which we will explore more in the section possible functional roles for spontaneous activity.

Together, recent work across species suggests that a subset of spontaneous neural patterns correspond to various behaviors in the absence or presence of sensory cues and also during decision-making tasks. Therefore, the term “spontaneous” activity for activity in the absence of sensory stimuli may be inaccurate, given the representations of non-sensory factors, such as movement, navigation, arousal, and vestibular signals. These non-sensory representations in sensory-driven neurons suggest that a major function of sensory areas is to integrate diverse sensory and non-sensory information to drive flexible behaviors. Do the representation of behaviors in sensory areas impair neurons’ abilities to encode sensory variables?

### SPONTANEOUS ACTIVITY IN MANY CASES IS ORTHOGONAL TO SENSORY-DRIVEN ACTIVITY

Like SA, sensory stimuli also activate a diverse set of neural patterns, and various studies have observed tens to hundreds of significant dimensions in flies, zebrafish, mice, and primates (Avitan et al., 2017; Cowley et al., 2016; Kong et al., 2022; Murthy et al., 2008; Stringer et al., 2019a). Many neurons are active during both spontaneous and sensory-driven activity, but it appears that the neurons present in a specific SA pattern are not all driven by the same sensory stimulus. In other words, the SA neural subspace appears to be orthogonal to the sensory-driven neural subspace (see Box 3). For example, in the visual cortex of mice, neurons driven by the same behaviors during SA are tuned to various visual stimuli during passive stimulus viewing; therefore, the representations of behaviors and visual stimuli are orthogonal (Stringer et al., 2019b; Figures 2C and 2D). Additionally, in an associative learning task, the representations of behavioral state are orthogonal to the neural representation of

---

| Study                  | Species | Brain area       | # of neurons | Dimensions at | % variance explained | Cross-validated |
|------------------------|---------|------------------|--------------|---------------|----------------------|----------------|
| Stringer et al., 2019b| mouse   | visual cortex    | ~10,000      | 128           | 86% of shared, 31% of raw | yes            |
| Stringer et al., 2019b| mouse   | brain-wide ephys | ~3,000       | 128           | 35% of raw           | yes            |
| Lanore et al., 2021   | mouse   | cerebellum       | ~300         | 22            | 34% of raw           | yes            |
| Avitan et al., 2017   | zebrafish| optic tectum     | ~100         | 50            | 80% of raw           | no             |
| MacDowell and Buschman| mouse   | dorsal cortex    | widefield    | 14            | 75% of raw           | yes            |
| Smith et al., 2018    | ferret  | visual cortex    | widefield    | 13            | 75% of raw           | no             |
| Gotts et al., 2020    | human   | whole-brain      | widefield    | 56            | 90% of raw           | no             |

Table 1. Estimated dimensionality of spontaneous neural activity in large-scale recordings demonstrates the high-dimensional nature of spontaneous activity.
The cortex operates in multiple states, which are characterized by varying amounts of fluctuation in spontaneous population activity. The classical desynchronized and synchronized states are associated with the awake or sleep states and constitute two points on a continuum of states (Buzsáki, 2006; Steriade, 2003). The desynchronized state is characterized with rapid local patterns, and the synchronized state is characterized with low-frequency, large-scale synchronized rhythms of neuronal activity. Several underlying cellular mechanisms have been shown to control these variations. Cortical neurons change their intrinsic firing patterns during shifts in the level of vigilance, where changes in membrane potential shift neurons from being intrinsically bursting to regularly spiking (Steriade, 2001; Steriade et al., 2001). The thalamus plays a critical role in generating synchronized fluctuations. Synaptic activity arising locally in the thalamus or in distant structures have a substantial impact on intrinsic properties of thalamic neurons as well as their oscillatory activity (Destexhe, 2009; Destexhe et al., 1999; Haider and McCormick, 2009; McCormick and Bal, 1997). High-frequency cortical correlated synaptic activity observed during the awake state (Steriade, 1978) modifies the biophysical properties of cortical neurons and affects their integrative properties (Bermander et al., 1991; Destexhe et al., 1999; Holmes and Woody, 1989). In addition, long-range synaptic networks were shown to generate different types of brain rhythms and control their duration (McCormick and Pape, 1990). Brain states are also controlled through slow-acting modulators, mostly in the brainstem or hypothalamic nuclei that have broad projections as well as local and long-range rapidly acting excitatory and inhibitory neurotransmitter pathways (Lee et al., 2014; McCormick and Bal, 1997; Steriade et al., 1993; Thiele and Beligrove, 2018; van den Brink et al., 2019; Zagha and McCormick, 2014).

Neural activity also rapidly changes during arousal-related movements like locomotion or whisking. This rapid change in brain activity coincides with changes in the intrinsic properties of single neurons. In awake mice, membrane potential oscillations are associated with quiet wakefulness and stable depolarization with active whisking and locomotion (Crochet and Petersen, 2006; McGinley et al., 2015a; Petersen, 2019; Polack et al., 2013; Poulet and Crochet, 2019). Outside periods of walking and whisking, there are also periodic bouts of depolarization and suppression of spontaneous population activity associated with arousal, as measured by increases in pupil diameter (McGinley et al., 2015a, 2015b; Vinck et al., 2015). This suggests that inputs to excitatory neurons alone do not explain behavior-related firing patterns. Instead, there may be increased drive to both excitatory and inhibitory neurons or other changes in intrinsic properties that cause a balancing of membrane potentials near threshold (Kanashiro et al., 2017; Stringer et al., 2016).

**Box 2. Cellular and local network mechanisms of spontaneous activity generation**

The cortex operates in multiple states, which are characterized by varying amounts of fluctuation in spontaneous population activity. The classical desynchronized and synchronized states are associated with the awake or sleep states and constitute two points on a continuum of states (Buzsáki, 2006; Steriade, 2003). The desynchronized state is characterized with rapid local patterns, and the synchronized state is characterized with low-frequency, large-scale synchronized rhythms of neuronal activity. Several underlying cellular mechanisms have been shown to control these variations. Cortical neurons change their intrinsic firing patterns during shifts in the level of vigilance, where changes in membrane potential shift neurons from being intrinsically bursting to regularly spiking (Steriade, 2001; Steriade et al., 2001). The thalamus plays a critical role in generating synchronized fluctuations. Synaptic activity arising locally in the thalamus or in distant structures have a substantial impact on intrinsic properties of thalamic neurons as well as their oscillatory activity (Destexhe, 2009; Destexhe et al., 1999; Haider and McCormick, 2009; McCormick and Bal, 1997). High-frequency cortical correlated synaptic activity observed during the awake state (Steriade, 1978) modifies the biophysical properties of cortical neurons and affects their integrative properties (Bermander et al., 1991; Destexhe et al., 1999; Holmes and Woody, 1989). In addition, long-range synaptic networks were shown to generate different types of brain rhythms and control their duration (McCormick and Pape, 1990). Brain states are also controlled through slow-acting modulators, mostly in the brainstem or hypothalamic nuclei that have broad projections as well as local and long-range rapidly acting excitatory and inhibitory neurotransmitter pathways (Lee et al., 2014; McCormick and Bal, 1997; Steriade et al., 1993; Thiele and Beligrove, 2018; van den Brink et al., 2019; Zagha and McCormick, 2014).

Neural activity also rapidly changes during arousal-related movements like locomotion or whisking. This rapid change in brain activity coincides with changes in the intrinsic properties of single neurons. In awake mice, membrane potential oscillations are associated with quiet wakefulness and stable depolarization with active whisking and locomotion (Crochet and Petersen, 2006; McGinley et al., 2015a; Petersen, 2019; Polack et al., 2013; Poulet and Crochet, 2019). Outside periods of walking and whisking, there are also periodic bouts of depolarization and suppression of spontaneous population activity associated with arousal, as measured by increases in pupil diameter (McGinley et al., 2015a, 2015b; Vinck et al., 2015). This suggests that inputs to excitatory neurons alone do not explain behavior-related firing patterns. Instead, there may be increased drive to both excitatory and inhibitory neurons or other changes in intrinsic properties that cause a balancing of membrane potentials near threshold (Kanashiro et al., 2017; Stringer et al., 2016).

A conditioned auditory stimulus in the amygdala (Gründemann et al., 2019). Orthogonality of spontaneous and sensory-driven patterns also exists in the optic tectum of larval zebrafish, where neurons that are co-active during SA have varied visual tuning (Avitan et al., 2021; Tripplett et al., 2020). If sensory-driven and behavioral patterns were closely aligned, i.e., neurons that were active during a specific stimulus presentation were also always active during a specific behavior, then a downstream area from visual cortex would not be able to distinguish between stimulus presentations and behaviorally driven activity. Therefore, the separation of behavioral and stimulus neural subspaces enables high-fidelity decoding from neural populations, regardless of the animal’s actions (Goris et al., 2017; Montijn et al., 2016; Stringer et al., 2021; Figure 2C).

During decision-making tasks, several dimensions of internally generated activity in sensory areas correspond to representations of choice and behavioral context (Hajnal et al., 2021; Kim and Shadlen, 1999; Lee et al., 2020; Musall et al., 2019; Reinert et al., 2021; Salkoff et al., 2020; Steinmetz et al., 2019). This internally generated activity is also represented in different neural subspaces from sensory-driven activity. For instance, in the mouse visual cortex, visual information and task context (auditory versus visual) are optimally decoded from the neural population using orthogonal vectors (Hajnal et al., 2021; Figure 2E). In macaque middle temporal visual area (MT), visual information and choice information are represented in orthogonal subspaces (Zhao et al., 2020). Other studies in mouse and macaque primary visual areas have suggested that choice-specific information is not present before the behavioral choice in primary visual areas (Goris et al., 2017; Steinmetz et al., 2019; Stringer et al., 2021); instead, non-stimulus-related activity during a behavioral task may be related to the movements of the animal (Musall et al., 2019; Salkoff et al., 2020). Together, a recent and growing body of work across species, brain areas, and behavioral tasks reports an orthogonal relationship between spontaneous and sensory-driven patterns.

This distinction between sensory-driven and non-sensory neural patterns in primary sensory areas enforces more accurate sensory coding by keeping the variability originating from non-sensory factors in a different neural subspace from sensory-driven activity. In addition, this orthogonality may allow modulatory circuits access to sensory representations for attentional or contextual modulation (Dubreuil et al., 2021). Since behaviorally driven spontaneous patterns are orthogonal to sensory-driven patterns, neurons represent many possible behavior-stimulus combinations (Stringer et al., 2019b), and these integrated representations may provide a scaffold for learning.

**POSSIBLE FUNCTIONAL ROLES FOR SPONTANEOUS ACTIVITY**

In the previous sections, we collected evidence showing that spontaneous and sensory-driven patterns of neural activity grow more distant over development and become distinct in the mature animals. We suggest that this dissimilarity enables a high-fidelity readout of sensory-driven patterns, which is not disturbed by spontaneous patterns. It is unclear, however, that...
In (C), the stimulus vectors $v_{stim1}$ and $v_{stim2}$ are orthogonal to the behavioral neurons 1 and 2 and negative for 3 and 4.

The orthogonality between these vectors was also observed by behavior (whisking); hence, the whisking vector $v_{whisk}$ is positive for neurons 1 and 2 are more active during whisking, and neurons 3 and 4 are less active during whisking (bottom traces). Neurons 1 and 2 are more active during whisking, and neurons 3 and 4 are less active during whisking; hence, the whisking vector $v_{whisk}$ is positive for neurons 1 and 2 and negative for 3 and 4.

The discriminant direction in neural population space which best distinguishes these vectors was also observed experimentally in mice (Stringer et al., 2019b).

The discriminant direction in neural population space which best distinguishes the context of the task (visual or auditory) in a context-dependent behavioral task in mice (Hajnal et al., 2021).

**Figure 2. Behavioral modulation and orthogonality of spontaneous and evoked pattern**

(A) The response of the stimulus vector (defined as the activity of the vector averaged during each stimulus presentation) was found to be multiplicatively modulated by behavioral state as defined by running speed in mice (Dadarlat and Stryker, 2017; Niell and Stryker, 2010) (data from Stringer et al., 2019b).

(B) Each dot represents the response of stimulus vectors for stimulus 1 and 2 for each presentation of stimulus 1 (blue) and stimulus 2 (green). A one-dimensional multiplicative gain model fit to the neural data (red line) explained most of the variability in these vectors’ responses (around 90%, see Stringer et al., 2019b).

(C) A toy schematic of the activity of 4 neurons which are additively modulated by behavior (whisking) and driven by stimuli (either stimulus 1 or stimulus 2). Neurons 1 and 3 are driven by stimulus 1; hence, the stimulus vector for stimulus 1 $v_{stim1}$ is positive for those neurons. The activity of the stimulus vector is defined as the neural activity projected onto that vector (bottom traces). Neurons 1 and 2 are more active during whisking, and neurons 3 and 4 are less active during whisking; hence, the whisking vector $v_{whisk}$ is positive for neurons 1 and 2 and negative for 3 and 4.

(D) In (C), the stimulus vectors $v_{stim1}$ and $v_{stim2}$ are orthogonal to the behavioral vector $v_{whisk}$. The orthogonality between these vectors was also observed experimentally in mice (Stringer et al., 2019b).

(E) The discriminant direction in neural population space which best distinguishes between visual stimuli was found to be orthogonal to the discriminant direction which best distinguishes the context of the task (visual or auditory) in a context-dependent behavioral task in mice (Hajnal et al., 2021).

We propose that the presence of SA patterns alongside sensory-driven patterns may facilitate the learning of associations between sensory inputs and other correlates such as behavior or internal state. The fly mushroom body is an example of a brain area that multiplexes sensory, behavioral, and reward information to perform associative learning. In the fly mushroom body, Kenyon cells are sparsely driven by odor signals (Murthy et al., 2008), and dopaminergic neurons are modulated by various behaviors and contexts such as locomotion, starvation, and mating experience (Siju et al., 2020; Zolin et al., 2021). The dopaminergic neurons modulate the synapses from Kenyon cells onto the output neurons of the mushroom body and also modulate the output neurons themselves. The mushroom body output neurons encode different valences and drive behaviors such as avoidance of negative valence stimuli or attraction to positive valence stimuli (Aso et al., 2014; Cohn et al., 2015; Hige et al., 2015; Modí et al., 2020; Oswald and Waddell, 2015; Zolin et al., 2021). The activation of dopaminergic neurons after a specific odor leads to changes in synapses from Kenyon cells to mushroom body output neurons, supporting the use of behavioral and valence signals to form specific odor memories (Cohn et al., 2015; Handler et al., 2019; Hige et al., 2015).

Associations between stimuli and behaviors may also directly occur in the sensory cortical areas of mammals. For example, after a mouse learns either an active decision-making task or a passive association, there is an increase in the number of visual cortical neurons that respond to the rewarded visual stimulus compared with the unrewarded stimulus (Henschke et al., 2020; Pakan et al., 2018) (see also Clopath et al., 2017; Keller et al., 2017). If these rewarded stimulus neurons also drive the mouse to perform the rewarded behavior, then the mouse’s performance would improve as these neurons increase their activity. The circuit may therefore receive reward-related signals to increase the activity of these neurons that are linked to a certain behavior and stimulus, resulting in the learning of the task. Indeed, certain cortical neurons in sensory areas can directly drive behaviors in rodents such as corticostriatal neurons, i.e., neurons that project to the striatum (Cox and Witkin, 2019; Shepherd, 2013). For example, the activation of corticostriatal neurons in auditory cortex can bias the choices of rats in an auditory discrimination task (Znamenskiy and Zador, 2010). The shaping of associations between sensory stimuli and behavioral decisions directly in sensory areas may be advantageous due to the high-dimensional nature of sensory representations in these areas compared with downstream brain regions.

Together, these hypotheses suggest that learning would alter sensory representations in primary sensory areas such that orthogonality between sensory and behavioral variables would no longer be maintained. The breaking of orthogonality for learned stimuli may enable faster responses to learned stimuli, rather than sending the stimulus and behavioral information to association areas.
CONCLUDING REMARKS AND FUTURE PERSPECTIVES

SA is a fundamental property of the circuit observed from the very early days of circuit assembly. Although early SA is known to guide appropriate circuit wiring, the role of SA in the wired behaving circuit is unknown. During development, SA also undergoes substantial changes, such as an increase in dimensionality and in behavioral correlation. The acquisition of these properties that are maintained in the mature circuit suggests that these properties serve a function. The high-dimensional nature of SA in sensory areas implies that SA can store many internal and external variables. Some of these variables include behaviors, choice information, and task context. The combination of this crucial information with sensory information may be essential for flexible sensory processing. The maintenance of SA patterns in orthogonal representations to sensory representations keeps sensory coding performance intact while instructing adaptive behaviors.

Although little is known about the role of SA in association cortical areas, SA in these areas is also reported to be modulated by behavior (Musall et al., 2019; Salkoff et al., 2020; Steinmetz et al., 2019; Stringer et al., 2019b). In mice, neural activity in these areas also reflects sensory, context, and choice variables in decision-making tasks (Akrami et al., 2018; Erlich et al., 2015; Katz et al., 2016; Lee et al., 2020; Licata et al., 2017). In primates, intraparietal association areas are modulated by sensory, motor, and vestibular inputs (Chen et al., 2011; Colby et al., 1996; Linden et al., 1999). However, perturbing the activity in association areas does not always alter the behavioral choice of the animal (Erlich et al., 2015; Katz et al., 2016; Zhong et al., 2019).

More research in both sensory and association areas is required to determine the role of SA patterns in learning decision-making tasks. We suggest that recording spontaneous and sensory-driven activity throughout the learning process may provide insights into how SA can shape sensory responses and decision-making across brain areas.

Recent techniques for recording neural activity in the awake animal, such as large-scale fluorescent calcium imaging and Neuropixels recordings, now allow the inspection of hundreds to thousands of neurons during spontaneous and sensory-driven activities, providing new opportunities to study the role of SA in complex behaviors and decision-making.
activity, alongside new techniques for monitoring behaviors (Datta et al., 2019; Hausmann et al., 2021). These techniques create the opportunity for new experiments and theories to dissect the functional role of SA in neural computation.

ACKNOWLEDGMENTS

We thank Mehrab Modi for comments on the manuscript. This research was funded by the Israel Science Foundation (ISF grant no. 1884/20) and the Howard Hughes Medical Institute at the Janelia Research Campus.

REFERENCES

Abdolrahmani, M., Lyaminin, D.R., Aoki, R., and Benuccci, A. (2021). Attention separates sensory and motor signals in the mouse visual cortex. Cell Rep. 36, 109377.

Abeles, M. (1982). Local Cortical Circuits: an Electrophysiological Study. Studies of Brain Function (Springer-Verlag).

Ackman, J.B., Burbridge, T.J., and Crair, M.C. (2012). Retinal waves coordinate patterned activity throughout the developing visual system. Nature 490, 219–225.

Ackman, J.B., and Crair, M.C. (2014). Role of emergent neural activity in visual map development. Curr. Opin. Neurobiol. 24, 166–175.

Akrami, A., Kopec, C.D., Diamond, M.E., and Brody, C.D. (2018). Posterior parietal cortex repre-sents sensory history and mediates its effects on behaviour. Nature 554, 368–372.

Albert, M.V., Schnabel, A., and Field, D.J. (2008). Inneate visual learning through spontaneous activity patterns. PLoS Comp. Biol. 4, e1000137.

Allen, W.E., Chen, M.Z., Pichamoothy, N., Tien, R.H., Pachitariu, M., Luo, L., and Deisseroth, K. (2019). Thirst regulates motivated behavior through modulation of brainwide neural population dynamics. Science 364, 253.

Arroyo, D.A., and Feller, M.B. (2016). Spatiotemporal features of retinal waves instruct the wiring of the visual circuitry. Front. Neural Circuits 10, 54.

Aso, Y., Sitaraman, D., Ichinose, T., Kaun, K.R., Vogt, K., Bellart-Guérin, G., Piaçais, P.-Y., Robie, A.A., Yamagata, N., Schnaitmann, C., et al. (2014). Mushroom body output neurons encode valence and guide memory-based action selection in Drosophila. Elife 3, e04580.

Avitan, L., Pujic, Z., Möller, J., Zhu, S., Sun, B., and Goodhill, G.J. (2021). Spontaneous and evoked activity patterns diverge over development. eLife 10, e61942.

Avitan, L., Pujic, Z., Möller, J., Van De Poll, M., Sun, B., Teng, H., Amor, R., Scott, E.K., and Goodhill, G.J. (2017). Spontaneous activity in the zebrafish tectum reorganizes over development and is influenced by visual experience. Curr. Biol. 27, 2407–2419.e1.

Ayaz, A., Saleem, A.B., Schölvinck, M.L., and Carandini, M. (2013). Locomotion controls spatial integration in mouse visual cortex. Curr. Biol. 23, 890–894.

Azensthatt, I., Meirovithz, E., Edelman, H., Werner-Reiss, U., Bienenstock, E., Abeles, M., and Slovin, H. (2009). Precise spatiotemporal patterns among visual cortical areas and their relation to visual stimulus processing. J. Neurosci. 30, 11232–11245.

Bartoszek, E.M., Ostenrath, A.M., Jetti, S.K., Serneels, B., Mutlu, A.K., Chau, K.T.P., and Yaksi, E. (2021). Ongoing habenular activity is driven by forebrain networks and modulated by olfactory stimuli. Curr. Biol. 31, 3861–3874.e3.

Benisty, H., Moberly, A.H., Lohani, S., Barson, D., Coifman, R.R., Mishne, G., Cardin, J.A., and Higley, M.J. (2021). Rapid fluctuations in functional connectivity of cortical networks encode spontaneous behavior. Preprint at bioRxiv. https://doi.org/10.1101/2021.08.15.456990.

Berkes, P., Orbán, G., Lengyel, M., and Fiser, J. (2011). Spontaneous cortical activity reveals hal- marks of an optimal internal model of the environment. Science 331, 83–87.

Bernander, O., Douglas, R.J., Martin, K.A., and Koch, C. (1991). Synaptic background activity influences spatiotemporal integration in single pyramidal cells. Proc. Natl. Acad. Sci. USA 88, 11569–11573.

Bouvier, G., Senzai, Y., and Scanziani, M. (2020). Head movements control the activity of primary visual cortex in a luminance-dependent manner. Neuron 108, 500–511.e5.

Busse, L., Cardin, J.A., Chiappe, M.E., Halassa, M.M., McGinley, M.J., Yamashita, T., and Saleem, A.B. (2017). Sensation during active behaviors. J. Neurosci. 37, 10826–10834.

Butts, D.A., Kanold, P.O., and Shatz, C.J. (2007). A burst-based “Hebbian” learning rule at retino- geniculate synapses links retinal waves to activity-dependent refinement. PLoS Biol. 5, e61.

Buzsáki, G. (2006). Rhythms of the Brain (Oxford University Press).

Chen, A., DeAngelis, G.C., and Angelaki, D.E. (2011). Representation of vestibular and visual cues to self-motion in ventral intraparietal cortex. J. Neurosci. 31, 12036–12052.

Chen, Y., Geisler, W.S., and Seidemann, E. (2006). Optimal decoding of correlated neural population responses in the primate visual cortex. Nat. Neurosci. 9, 1412–1420.

Chiappe, M.E., Seelig, J.D., Reiser, M.B., and Jayaraman, V. (2010). Walking modulates speed sensitivity in drosophila motion vision. Curr. Biol. 20, 1470–1475.

Clancy, K.B., Orsolic, I., and Mрисic-Флugeot, T.D. (2019). Locomotion-dependent remapping of dis-tributed cortical networks. Nat. Neurosci. 22, 778–788.

Clopath, C., Bonhoeffer, T., Hübener, M., and Rose, T. (2017). Variance and invariance of neuronal long-term representations. Phil. Trans. R. Soc. B 372, 20160161.

Cohn, R., Morantte, I., and Ruta, V. (2015). Coordinated and compartmentalized neuromodulation shapes sensory processing in drosophila. Cell 163, 1742–1755.

Colby, C.L., Duhamel, J.-R., and Goldberg, M.E. (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. J. Neurophysiol. 76, 2841–2852.

Colonnese, M.T., and Phillips, M.A. (2018). Thalamocortical function in developing sensory circuits. Curr. Opin. Neurobiol. 52, 72–78.

Cowley, B.R., Smith, M.A., Kohn, A., and Yu, B.M. (2016). Stimulus-driven population activity patterns in macaque primary visual cortex. PLoS Comp. Biol. 12, e1005185.

Cox, J., and Witten, I.B. (2019). Striatal circuits for reward learning and decision-making. Nat. Rev. Neurosci. 20, 482–494.

Crochet, S., and Petersen, C.C.H. (2006). Correlating whisker behavior with membrane potential in barrel cortex of awake mice. Nat. Neurosci. 9, 608–610.

Dadarlat, M.C., and Stryker, M.P. (2017). Locomotion enhances neural encoding of visual stimuli in mouse v1. J. Neurosci. 37, 3764–3775.

Datta, S.R., Anderson, D.J., Branson, K., Perona, P., and Leifer, A. (2019). Computational neuroethology: a call to action. Neuron 104, 11–24.

Destexhe, A. (2009). Self-sustained asynchronous irregular states and updated states in thalamic, cortical and thalamocortical networks of nonlinear integrate-and-fire neurons. J. Comput. Neurosci. 27, 493–506.

Destexhe, A., Contreras, D., and Steriade, M. (1999). Cortically-induced coherence of a thalamic-generated oscillation. Neuroscience 92, 427–443.

Dubreuil, A., Valente, A., Beiran, M., Mastrogiuseppe, F., and Ostojic, S. (2021). The role of population structure in computations through neural dynamics. Preprint at bioRxiv. https://doi.org/10.1101/2020.07.03.185942.

Engel, T.A., Steinmetz, N.A., Diesmann, M., Destexhe, A., and Slovin, H. (2001). Selective modulation of cortical state during spatial attention. Science 294, 1140–1144.

Engelhard, B., Finkelstein, J., Cox, J., Fleming, W., Jang, H.J., Ornelas, S., Koay, S.A., Thiberge, S.Y., Daw, N.D., Tank, D.W., et al. (2019). Specialized
coding of sensory, motor and cognitive variables in vta dopamine neurons. Nature 570, 509–513.

Erich, J.C., Brunton, B.W., Duan, C.A., Hanks, T.D., and Brody, C.D. (2015). Distinct effects of prefrontal and parietal cortex inactivations on an accumulation of evidence task in the rat. eLife 4, e05457.

Ferguson, K.A., and Cardin, J.A. (2020). Mechanisms underlying gain modulation in the cortex. Nat. Rev. Neurosci. 21, 80–92.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., and Raichle, M.E. (2009). The human brain is intrinsically organized into dynamical anticorrelated functional networks. Proc. Natl. Acad. Sci. 102, 9673–9678.

Fujitawa, T., Cruz, T.L., Bohnslav, J.P., and Chiappe, M.E. (2017). A faithful internal representation of walking movements in the drosophila visual system. Nat. Neurosci. 20, 72–81.

Gahtan, E., Tanger, P., and Baier, H. (2005). Visual prey capture in larval zebrafish is controlled by identified reticulospinal neurons downstream of the tectum. J. Neurosci. 25, 9294–9303.

Gao, P., Trautmann, E., Yu, B., Santhanam, G., Ryu, S., Shenoy, K., and Ganguli, S. (2017). A theory of multineuronal dimensionality, dynamics and measurement. Preprint at bioRxiv. https://doi.org/10.1101/214262.

Golshani, P., Gonçalves, J.T., Khoshkhoo, S., Mostany, R., Smirnakis, S., and Portera-Cailliau, G. (2009). Internally mediated developmental desynchronization of neocortical network activity. J. Neurosci. 29, 10890–10899.

Goris, R.L.T., Ziemba, C.M., Stine, G.M., Simoncelli, E.P., and Movshon, J.A. (2015). Temporal sensitivity of associative learning. Cell 162, 60–75.e19.

Han, F., Caporale, N., and Dan, Y. (2008). Reverberation of recent visual experience in spontaneous cortical waves. Neuron 60, 321–327.

Handler, A., Graham, T.G.W., Cohn, R., Morantte, I., Siliciano, A.F., Zeng, J., Li, Y., and Ruta, V. (2019). Distinct dopamine receptor pathways underlie the functional significance of decision-related activity in the primate dorsal stream. Nature 535, 285–288.

Keller, A.J., Houlton, R., Kampa, B.M., Lesica, N.A., Mnsic-Flogel, T.D., Keller, G.B., and Helmchen, F. (2017). Stimulus relevance modulates contrast adaptation in visual cortex. eLife 6, e21589.

Keller, G.B., and Mnsic-Flogel, T.D. (2018). Predictive processing: a canonical cortical computation. Neuron 100, 424–435.

Kenet, T., Bibitchkov, D., Tsodyks, M., Grivnald, A., and Arieli, A. (2003). Spontaneous emerging cortical representations of visual attributes. Nature 425, 954–956.

Kim, J.N., and Shadlen, M.N. (1999). Neural correlates of a decision in the dorsolateral prefrontal cortex of the macaque. Nat. Neurosci. 2, 176–185.

Kirkby, L.A., Sack, G.S., Firi, A., and Feller, M.B. (2013). A role for correlated spontaneous activity in the assembly of neural circuits. Neuron 80, 1129–1144.

Kong, N.C.L., Margalit, E., Gardner, J.L., and Norcia, A.M. (2022). Increasing neural network robustness improves match to macaque v1 eigenspectrum, spatial frequency preference and predictivity. PLoS Comp. Biol. 18, 1–25.

Lee, J.J., Krumin, M., Harris, K.D., and Carandini, M. (2020). Task specificity in mouse parietal cortex. Preprint at bioRxiv. https://doi.org/10.1101/2020.12.18.423543.

Leighton, A.H., and Lohmann, C. (2016). The wiring of developing sensory circuits—from patterned spontaneous activity to synaptic plasticity mechanisms. Front. Neural Circuits 10, 71.

Lanore, F., Cayco-Gajic, N.A., Gurnani, H., Coyle, D., and Silver, R.A. (2021). Cerebellar granule cell axons support high-dimensional representations. Nat. Neurosci. 24, 1142–1150.

Lee, A.M., Hoy, J.L., Bonci, A., Wilbrecht, L., Stryker, M.P., and Niell, C.M. (2014). Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. Neuron 83, 455–466.

Lew, J.J., Krimm, M., Harris, K.D., and Carandini, M. (2020). Task specificity in mouse parietal cortex. Preprint at bioRxiv. https://doi.org/10.1101/2020.12.18.423543.
MacDowell, C.J., and Buschman, T.J. (2020). Low-dimensional spatiotemporal dynamics underlie cortex-wide neural activity. Curr. Biol. 30, 2665–2680.e8.

Maimon, G. (2011). Modulation of visual physiology by behavioral state in monkeys, mice, and flies. Curr. Opin. Neurobiol. 21, 559–564.

Martini, F.J., Guillamín-Vivancos, T., Moreno-Juan, V., Valdeolmillos, M., and López-Benito, G. (2021). Spontaneous activity in developing thalamic and cortical sensory networks. Neurobiol. 109, 2519–2534.

McCormick, D.A., and Bal, T. (1997). Sleep and arousal: thalamocortical mechanisms. Annu. Rev. Neurosci. 20, 185–215.

McCormick, D.A., and Pape, H.C. (1993). Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. J. Physiol. 431, 291–318.

McGinley, M.J., David, S.V., and McCormick, D.A. (2015a). Cortical membrane potential signature of optimal states for sensory signal detection. Neuron 87, 179–192.

McGinley, M.J., Vincik, M., Reimer, J., Batista-Brito, R., Zagha, E., Cadwell, C.R., Tolias, A.S., Cardin, J.A., and McCormick, D.A. (2015b). Waking state: rapid variations modulate neural and behavioral responses. Neuron 87, 1143–1161.

Meister, M., Wong, R.O., Baylor, D.A., and Shatz, C.J. (1991). Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. Science 252, 939–943.

Miller, J.E., Ayzenshtat, I., Camillo-Reid, L., and Yuste, R. (2014). Visual stimuli recruit intrinsically generated cortical ensembles. Proc. Nat. Acad. Sci. USA 111, E4053–E4061.

Modi, M.N., Shuai, Y., and Turner, G.C. (2020). The Drosophila mushroom body: from architecture to algorithm in a learning circuit. Annu. Rev. Neurosci. 43, 465–484.

Mohajerani, M.H., Chan, A.W., Mohsenvand, M., LeDue, J., Liu, R., McVea, D.A., Boyd, J.D., Wang, Y.T., Reimers, M., and Murphy, T.H. (2013). Spontaneous cortical activity alternates between motifs defined by regional axonal projections. Nat. Neurosci. 16, 1426–1435.

Molnár, Z., Luhmann, H.J., and Kanold, P.O. (2020). Transient cortical circuits match spontaneous and sensory-driven activity during development. Science 370, eabb2153.

Montijn, J.S., Meijer, G.T., Lansink, C.S., and Pennartz, C.M. (2016). Population-level neural codes are robust to single-neuron variability from a multidimensional coding perspective. Cell Rep. 20, 2539–2548.

Montjijn, J.S., Meijer, G.T., Lansink, C.S., and Pennartz, C.M. (2016). Population-level neural codes are robust to single-neuron variability from a multidimensional coding perspective. Cell Rep. 20, 2539–2548.

Muzzu, T., and Saleem, A.B. (2021). Feature selectivity explains mismatch signals in mouse visual cortex. Preprint at bioRxiv. https://doi.org/10.1101/2021.04.12.439457.

Ni, A.M., Huang, C., Doiron, B., and Cohen, M.R. (2021). A general decoding strategy explains the relationship between behavior and correlated variability. Preprint at bioRxiv. https://doi.org/10.1101/2020.10.08.331850.

Niel, C.M., and Stryker, M.P. (2010). Modulation of visual responses by behavioral state in mouse visual cortex. Neuron 65, 472–479.

Okun, M., Steinmetz, N., Coissell, L., Iacaruso, M.F., Ko, H., Barthó, P., Moore, T., Hofer, S.B., Mrsic-Flogel, T.D., Carandini, M., and Harris, K.D. (2015). Diverse coupling of neurons to populations in sensory cortex. Nature 521, 511–515.

Omer, D.B., Fekete, T., Ulchini, Y., Hideshima, R., and Grinvald, A. (2019). Dynamic patterns of spontaneous ongoing activity in the visual cortex of anesthetized and awake monkeys are different. Cereb. Cortex 29, 1291–1304.

Ovald, D., and Waddell, S. (2015). Offatory learning skews mushroom body output pathways to steer behavioral choice in drosophila. Curr. Opin. Neurobiol. 35, 178–184.

Pakan, J.M.P., Currie, S.P., Fischer, L., and Rochefort, N.L. (2018). The impact of visual cues, reward, and motor feedback on the representation of behaviorally relevant spatial locations in primary visual cortex. Cell Rep. 24, 2521–2528.

Palm, G., Knoblauch, A., Hauser, F., and Schüz, A. (2014). Cell assemblies in the cerebral cortex. Biol. Cybern. 108, 559–572.

Pang, R., Lansdell, B.J., and Fairhall, A.L. (2016). Dimensionality reduction in neuroscience. Curr. Biol. 26, R656–R660.

Petersen, C.C.H. (2019). Sensorimotor processing in the rodent barrel cortex. Nat. Rev. Neurosci. 20, 533–546.

Pietri, T., Romano, S.A., Pérez-Schuster, V., Boulanger-Weill, J., Candat, V., and Sumbre, G. (2017). The emergence of the spatial structure of tectal spontaneous activity is independent of visual inputs. Cell Rep. 19, 939–948.

Polack, P.-O., Friedman, J., and Golshani, P. (2013). Cellular mechanisms of brain state-dependent gain modulation in visual cortex. Nat. Neurosci. 16, 1331–1339.

Poulet, J.F.A., and Crochet, S. (2019). The cortical states of wakefulness. Front. Syst. Neurosci. 12, 84.

Reintert, S., Hubener, M., Bonhoeffer, T., and Goltstein, P.M. (2021). Mouse prefrontal cortex represents learned rules for categorization. Nature 593, 411–417.

Ringach, D.L. (2009). Spontaneous and driven cortical activity: implications for computation. Curr. Opin. Neurobiol. 19, 439–444.

Rochefort, N.L., Garaschuk, O., Milos, R.-I., Narushima, M., Marandi, N., Pitcher, B., Kovalchuk, Y., and Konnerth, A. (2009). Sparserification of neuronal activity in the visual cortex at eye-opening. Proc. Natl. Acad. Sci. USA 106, 15049–15054.

Romano, S.A., Pietri, T., Pérez-Schuster, V., Jouary, A., Hądreych, M., and Sumbre, G. (2015). Spontaneous neuronal network dynamics Reveal circuit’s functional adaptations for behavior. Nature 85, 1070–1085.

Salkoff, D.B., Zagha, E., McCarthy, E., and McCormick, D.A. (2020). Movement and performance explain widespread cortical activity in a visual detection task. Cereb. Cortex 30, 421–437.

Schneider, D.M., Sundararajan, J., and Mooney, R. (2018). A cortical filter that learns to suppress the acoustic consequences of movement. Nature 561, 391–395.

Shepherd, G.M. (2013). Corticostriatal connectivity and its role in disease. Nat. Rev. Neurosci. 14, 278–291.

Siegel, F., Helm, J.A., Peters, J., and Lohmann, C. (2012). Peripheral and central inputs shape network dynamics in the developing visual cortex in vivo. Curr. Biol. 22, 252–258.

Siju, K.P., Stih, V., Almon, S., Gjorgjieva, J., Portugues, R., and Gruenwald Kadow, I.C. (2020). Valence and state-dependent population coding in dopaminergic neurons in the fly mushroom body. Curr. Biol. 30, 2104–2115.e4.

Smith, G.B., Hein, B., Whitney, D.E., Fitzpatrick, D., and Kaschube, M. (2018). Distributed network interactions and their emergence in developing neocortex. Nat. Neurosci. 21, 1600–1608.

Steinmetz, N.A., Zatka-Haas, P., Carandini, M., and Harris, K.D. (2019). Distributed coding of choice, action and engagement across the mouse brain. Nature 576, 266–273.

Steriade, M. (1993). Cortical long-axon cells and putative interneurons during the sleep-waking cycle. Behav. Brain Sci. 16, 465–485.

Steriade, M. (2001). Impact of network activities on neuronal properties in corticothalamic systems. J. Neurophysiol. 86, 1–39.

Steriade, M. (2003). Neuronal Substrates of Sleep and Epilepsy (Cambridge University Press).

Steriade, M., McCormick, D.A., and Sejnowski, T.J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. Science 262, 679–685.
Steriade, M., Timofeev, I., and Grenier, F. (2001). Natural waking and sleep states: a view from inside neocortical neurons. J. Neurophysiol. 85, 1969–1985.

Stringer, C., Michaelos, M., Tsyboulski, D., Lindo, S.E., and Pachitariu, M. (2021). High-precision coding in visual cortex. Cell 184, 2767–2778.e15.

Stringer, C., Pachitariu, M., Steinmetz, N., Carandini, M., and Harris, K.D. (2019a). High-dimensional geometry of population responses in visual cortex. Nature 577, 361–365.

Stringer, C., Pachitariu, M., Steinmetz, N., Reddy, C.B., Carandini, M., and Harris, K.D. (2019b). Spontaneous behaviors drive multidimensional, brain-wide activity. Science 364, 255.

Stringer, C., Michaelos, M., Tsyboulski, D., Lindo, S.E., and Pachitariu, M. (2021). High-precision coding in visual cortex. Cell 184, 2767–2778.e15.

Stringer, C., Michaelos, M., Tsyboulski, D., Lindo, S.E., and Pachitariu, M. (2021). High-precision coding in visual cortex. Cell 184, 2767–2778.e15.

Stringer, C., Pachitariu, M., Steinmetz, N., Carandini, M., and Harris, K.D. (2019a). High-dimensional geometry of population responses in visual cortex. Nature 577, 361–365.

Stringer, C., Pachitariu, M., Steinmetz, N., Reddy, C.B., Carandini, M., and Harris, K.D. (2019b). Spontaneous behaviors drive multidimensional, brain-wide activity. Science 364, 255.

Thiele, A., and Bellgrove, M.A. (2018). Neuromodulation of attention. Neuron 97, 769–785.

Thompson, A., Gribizis, A., Chen, C., and Crair, M.C. (2017). Activity-dependent development of visual receptive fields. Curr. Opin. Neurobiol. 42, 136–143.

Thompson, A.W., and Scott, E.K. (2016). Characterisation of sensitivity and orientation tuning for visually responsive ensembles in the zebrafish tectum. Sci. Rep. 6, 34887.

Triplett, M.A., Pujic, Z., Sun, B., Avitan, L., and Goodhill, G.J. (2020). Model-based decoupling of evoked and spontaneous neural activity in calcium imaging data. PLoS Comp. Biol. 16, e1008330.

van den Brink, R.L., Pfeffer, T., and Donner, T.H. (2019). Brainstem modulation of large-scale intrinsic cortical activity correlations. Front. Hum. Neurosci. 13, 340.

Vinck, M., Batista-Brito, R., Knoblich, U., and Cardin, J.A. (2015). Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. Neuron 86, 740–754.

Vladimirov, N., Wang, C., Hökendorf, B., Pujala, A., Tanimoto, M., Mu, Y., Yang, C.T., Wittenbach, J.D., Freeman, J., Preibisch, S., et al. (2018). Brain-wide circuit interrogation at the cellular level guided by online analysis of neuronal function. Nat. Methods 15, 1117–1125.

Warland, D.K., Huberman, A.D., and Chalupa, L.M. (2006). Dynamics of spontaneous activity in the fetal macaque retina during development of retinogeniculate pathways. J. Neurosci. 26, 5190–5197.

Williamson, R.S., Hancock, K.E., Shinn-Cunningham, B.G., and Polley, D.B. (2015). Locomotion and task demands differentially modulate thalamic audiovisual processing during active search. Curr. Biol. 25, 1885–1891.

Xu, H.P., Furman, M., Mineur, Y.S., Chen, H., King, S.L., Zenisek, D., Zhou, Z.J., Butts, D.A., Tian, N., Picciotto, M.R., and Crair, M.C. (2011). An instructive role for patterned spontaneous retinal activity in mouse visual map development. Neuron 70, 1115–1127.

Yuste, R. (2015). From the neuron doctrine to neural networks. Nat. Rev. Neurosci. 16, 487–497.

Zagha, E., and McCormick, D.A. (2014). Neural control of brain state. Current Opinion in Neurobiology 29, 178–186.

Zhang, R.-W., Li, X.-Q., Kawakami, K., and Du, J.-L. (2016). Stereotyped initiation of retinal waves by bipolar cells via presynaptic nmda autoreceptors. Nat. Commun. 7, 12650.

Zhao, Y., Yates, J.L., Levi, A.J., Huk, A.C., and Park, I.M. (2020). Stimulus-choice (mis)alignment in primate area mt. PLoS Comp. Biol. 16, e1007614.

Zhong, L., Zhang, Y., Duan, C.A., Deng, J., Pan, J., and Xu, N.-L. (2019). Causal contributions of parietal cortex to perceptual decision-making during stimulus categorization. Nat. Neurosci. 22, 963–973.

Znamenskiy, P., and Zador, A.M. (2013). Corticostratal neurons in auditory cortex drive decisions during auditory discrimination. Nature 497, 482–485.

Zolin, A., Cohn, R., Pang, R., Siliciano, A.F., Fairhall, A.L., and Ruta, V. (2021). Context-dependent representations of movement in drosophila dopaminergic reinforcement pathways. Nat. Neurosci. 24, 1555–1568.