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Editorial overview: Neurobiology of behavior

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Kay M Tye is an Associate Professor in the Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT. Her laboratory utilizes an interdisciplinary approach to functionally dissect neural circuits encoding emotional and motivational valence, with an emphasis on circuits perturbed in behaviors relevant to neuropsychiatric disease. She majored in Brain in Cognitive Sciences at MIT in 2003. She received her PhD from UCSF for her work on understanding the neural dynamics during associative learning using *in vivo* electrophysiological recordings in freely-moving rodents and the synaptic changes that occur with learning using *ex vivo* whole-cell patch-clamp recordings in brain slices. Her postdoctoral training at Stanford focused on developing and optimizing optogenetic tools. In 2011, she pioneered the use of projection-specific optogenetic manipulations, and continues to integrate such approaches along with synaptic physiology and large-scale *in vivo* electrophysiology and imaging techniques.

The study of neurobiology of behavior is a highly multi-disciplinary area and intersects with other disciplines studying human and animal behaviors including ethology, psychology, cognitive science, economics, artificial intelligence and clinical science. A common goal, however, would be to elucidate how behaviors are generated in terms of the structure and function of neural circuits. How do different cell types and their connectivity underlie behavior? How do properties of neurons and synapses affect the function of a neural circuit? An ultimate goal would be to derive principles regarding how neural circuits work and how they control behavior in healthy as well as disordered brains.

Although this is an enormous undertaking, the field of neurobiology has made revolutionary changes accelerated by the development of new tools. With the advent of modern neuroscience tools, neurobiologists can now perform the types of experiments that previous researchers could only dream of [1]. These tools have allowed us to monitor and manipulate the activity of neurons in behaving animals with unprecedented precisions. New tools have allowed us to identify connectivity of neurons with greater precisions. These studies have made various novel findings but also revealed various new challenges that the field faces. In this issue, we asked experts who have contributed to recent progress toward understanding how neural circuits regulate behaviors. We hope that these reviews will provide not only summaries of previous work but also help outlook what findings or research areas to come in the future.

New tools and behavioral paradigms

The development of new technologies has dramatically changed the landscape of neurobiological experiments. First, experiments using rodents and other genetically-tractable animals performing complex tasks have become more common. Second, while novel tools have led to unprecedented results with greater precision and specificity, the field has begun to evaluate the pros and cons of novel as well as more conventional methodologies. Although addressing this completely would be impossible in just a few papers, two papers in this issue aim to facilitate discussion on these topics.

Neuroscientists have long debated how to establish a ‘causal’ link between neuronal activity and behavior. It has been acknowledged that it is important to use carefully designed behavioral paradigms, and to draw conclusions taking into account multiple lines of supporting evidence. For instance, the gold standard of causality had been developed in studies of sensory systems that combined psychophysical behavioral paradigms, neurobiological experiments (not only manipulating but also monitoring endogenous neuronal activity), and simple models or theories regarding quantitative relationships between neuronal activity and behavior [2].

For the type of experiments discussed above (i.e. ‘causality’ experiments in sensory systems), non-human primate studies had been the dominant experimental paradigms, due largely to the ability to train these animals in sophisticated behavioral paradigms. Earlier efforts, however, enabled us to adapt comparable behavioral paradigms to rodents (e.g. [3–5]). On the other hand, there have also been some concerns in using these well-constrained behavioral paradigms. Training animals in these paradigms often requires extensive training (sometimes months) using unnatural

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behaviors. It has been argued that the results obtained using these paradigms may not reflect how the brain operates in a 'natural' behavioral condition. Other rodent experiments have used behaviors that are more 'natural' to the animals, such as spatial navigation, reflexive responses, or innate behaviors. The behavioral paradigms that rely on more 'natural' behaviors might be advantageous from some viewpoints. For instance, less training is necessary, and it likely taps onto 'natural' brain mechanisms. However, some of these behaviors are harder to quantify, and can be difficult to align with simple models or theories. [Luaviet, Ehrich and Churchland \(2018\)](#) discuss the challenge of how to design behavioral paradigms, using studies of decision-making in rodents as an example. They discuss the pros and cons of different approaches, and propose three axes — ethological, complexity and sensory motor compatibility — in evaluating designs of behavioral paradigms.

With new tools such as optogenetics and pharmacogenetics, we can now activate or inactivate neurons with greater temporal precision and cell-type specificity. Although studies using these new tools have provided novel insights addressing 'causality', recent studies have also identified interpretational difficulties in these studies. For one, neurons are connected in a complex manner, and form a highly dynamic system. Therefore, manipulation of one population of neurons can cause rippling effects on the activity of other neurons in a highly dynamic manner (e.g. [6]). Furthermore, the brain has various compensatory mechanisms at different timescales. The field, thus, needs conceptual developments regarding how to evaluate and interpret the effect of manipulations. [Wolff and Olveczky \(2018\)](#) together with other recent articles [7,8], provide important insights based on experimental data, emphasizing holistic approaches integrating complementary methods. As [Luaviet et al. \(2018\)](#) emphasizes, a choice of behavioral paradigm depends on particular questions in each study. There is also a balance between hypothesis-driven versus data-driven approaches. Although the above discussion may emphasize theory-guided, hypothesis-driven approaches, the conclusions obtained from hypothesis-driven approaches can sometimes be narrowly constrained or become largely confirmatory in nature.

Here our aim is not to provide one answer to the above questions. Instead, this volume contains overviews on recent progress in the neurobiology of behavior. Our hope is to showcase a spectrum of studies that spans across the 'axes' both in terms of behaviors and techniques (including studies in humans and computational modeling). The landscape of neuroscience is rapidly changing. We hope that the papers in this volume provide a broad perspective on the field, and inform our outlook on future developments in the field of neurobiology.

Behavioral modulations of information processing

Sensory information guides behaviors. Neuroscientists have studied how sensory information is represented and transformed in the brain while the information travels through a 'sensorimotor chain' to control behaviors. However, these 'chains' are not static. The same sensory input may trigger different behavioral outputs depending on an animal's needs or behavioral context. How do behavioral contexts modulate or 'gate' information flows in the brain? This question has long been studied, for instance, in the context of attention [9,10]. Recent studies, using rodent models, have begun to elucidate detailed neural circuit mechanisms at the level of cortical microcircuit as well as global brain network. [Angeloni and Geffen \(2018\)](#) discuss recent progress in the auditory system. These studies have elucidated a role for specific inhibitory interneurons in modulating sensory responses in the

neocortex. Burgess, Livneh, Ramesh and Andermann (2018) summarize recent studies on how motivational drives such as hunger modulate information processing in the visual cortex and beyond. These studies highlight interactions at a global network level: hunger-related signals originating in the hypothalamus affect neural activities in other subcortical areas including the amygdala, which then modulate information processing in higher visual association areas and the insular cortex.

A challenge in neuroscience is to obtain ‘principles’ by which the brain or a neural circuit operates, based on experimental results such as those discussed in the preceding two papers. Can we find a common or recurring computation underlying specific brain functions? If so, how is such a computation implemented in neural circuits? Can we find a circuit ‘motif’ that is suited to perform such a computation? Why is a particular implementation or motif chosen among other potential solutions? Wang and Yang (2018) provide their perspectives on these points with regard to ‘pathway gating’ in the brain, particularly focusing on a circuit motif — disinhibitory circuits — that involves dendritic inhibition through a specific type of inhibitory neuron (somatostatin-positive neurons) in the neocortex.

Reinforcement learning

One of the successful theories that provide a mechanism underlying behaviors is reinforcement learning [11]. Reinforcement learning theories provide an algorithm for trial-and-error learning and action selection, developed in the field of artificial intelligence, with its basic ideas rooted in animal learning theories [12,13]. A critical step in reinforcement learning is to predict future rewards (and punishments) based on the current ‘state’ that an agent occupies. An agent then chooses an appropriate action based on its predictions. The basic algorithm used in reinforcement learning is to update these predictions when a prediction does not match reality, that is, when there is a discrepancy between prediction and actual outcomes (i.e. ‘prediction error’). It has been shown that dopamine neurons in the midbrain exhibit firing patterns that resemble reward prediction errors (RPEs) [14–16]. In this volume, Stauffer (2018) provide an overview of how classic studies on dopamine neurons as well as recent studies using modern tools have contributed to establish this core idea. Furthermore, Stauffer (2018) extend his discussion to recent findings that dopamine RPEs approximate subjective values or ‘utility’ formulated in economic decision theories, and to studies addressing neural circuit mechanisms regarding how RPEs are calculated in the first place.

Although much research on reinforcement learning has been in the context of reward, punishment is an equally important consideration in reinforcement learning. These theories also extend to aversive prediction error, which is

relevant in the well-studied behavioral paradigm of Pavlovian fear conditioning [13,17]. Johansen and Ozawa (2018) discuss the circuits that mediate fear conditioning and associative learning framed in the context of aversive prediction error. Johansen and Ozawa identify circuits that are largely distinct from those implicated in detecting and representing RPEs, including the lateral amygdala, central amygdala, locus coeruleus and periaqueductal gray.

Prediction of future reward (and punishment) guides action selection as well as the calculation of RPEs. Recent studies have highlighted distinct mechanisms for predicting reward. In the original reinforcement learning models, reward predictions were made based on direct associations between states and rewards (model-free mechanisms). However, recent data have highlighted that reward prediction often involves inference from ambiguous information or predictions based on more abstract ‘models’ of the environment or the task at hand. Langdon, Sharpe, Schoenbaum and Niv (2018) reviews new experimental results and theories indicating the importance of these inference or model-based reward predictions as well as how the animal learns a ‘model’ to begin with.

Song learning in songbirds has long been a great model for trial-and-error learning. Indeed, this is one of the earliest systems to which reinforcement learning models have been applied [18]. Imitating a father bird’s song requires storing a memory of the ‘tutor’ song, reproducing it, and evaluating whether it matched the tutor song. Birds learn to sing by repeatedly practicing without explicit external rewards. Recent data suggest that song learning involves ‘internal reward’ that is signaled by dopamine [19]. The distinct features of learning in songbirds have presented unique problems as well as novel insights into general principles of reinforcement learning [20,21]. Mackevicius and Fee (2018) presents novel perspectives on song learning. One way to model song learning is to view each moment during the song as a ‘state’ in reinforcement learning. A song is constructed over a sequence of states, and the states are represented by sequential activation of neurons in the premotor area, HVC. The pattern of HVC activity is then associated with proper motor outputs through reinforcement learning. Mackevicius and Fee (2018) discusses how state representations in HVC may be formed through interactions with the auditory system that may store a memory about the tutor song, and through synaptic plasticity in HVC.

Another animal model that has been used for learning, in particular, associative learning, is the fruit fly *Drosophila melanogaster*. Here dopamine also plays important roles. Studies in flies have revealed the existence of multiple dopamine systems, each with a distinct type of signal — reward, punishment, novelty, etc. Recent studies showed that seemingly ‘simple’ associative learning is regulated

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by layers of mechanisms that occur on short and long timescales. [Paola, Felsenberg and Waddell \(2018\)](#) discusses roles of recurrent connections in reverberating neural activities, connecting reward information at distinct timescales (e.g. immediate taste feedback versus later nutritional impact), and re-evaluating and reconsolidating associative memories. The empirical results discussed in this review provide richer biological mechanisms that are critical, yet often overlooked by simpler reinforcement learning models.

Decision-making

Decision-making involves evaluating and choosing between different options, and executing an appropriate action. Recent studies have begun to reveal neural circuit mechanisms underlying decision making. These processes can be broken down into multiple components. [Rich, Stoll and Rudebeck \(2018\)](#) discusses neural processing while an animal evaluates different options. Evaluation of options often requires shifting attention between different options and adapting to changing behavioral needs. They discuss how neurons in the orbitofrontal cortex modulate their activity dynamically within each evaluation period or over a longer timescale where behavioral contexts are changed.

As a decision is formed, the animal has to translate it into an appropriate action to achieve its goal. This process requires winner-take-all dynamics, often modeled by a neural integrator (evidence accumulation) or attractor dynamics [22]. When an action needs to be withheld until the right moment, the animal has to keep the relevant information in short-term memory, and prepare for a desired motor output. Neural processes involved in the preparation and execution of motor actions has been studied in various animals including humans, non-human primates and rodents. More detailed views at the neural circuit level have been obtained recently in mice and, even simpler organisms such as zebrafish and fruit flies. [Svoboda and Li \(2018\)](#) summarizes recent progress in motor preparation in non-human primates and mice. Motor preparation involves neural circuit dynamics in a ‘motion-null space’, whereby activity patterns evolve without affecting immediate motor outputs. Modern tools have allowed researchers to elucidate multiple brain areas and interactions between them that together regulate these attractor-like dynamics in mammalian brains. [Koyama and Pujala \(2018\)](#) discusses neural circuit motifs subserving distinct, yet related, computations. They start by describing a ‘circuit motif’ involved in escape behavior in fish — a life-or-death decision in this species. This simple circuit motif — mutual inhibition of lateral inhibition — achieves point attractor dynamics. This circuit motif has been found in neural circuits involved in different functions and animal species, including selective attention in barn owls and direction tuning in the mouse retina, suggesting that this circuit motif forms a

building block to achieve common computational goals such as sharpening outputs in the face of noisy inputs.

Hippocampus: representation of spatial maps and beyond

The idea of model-based control of behavior originates in the ‘cognitive map’ proposed by Tolman [23]. Decades of work in human patients and animal models have shown that the hippocampus plays a critical role in episodic memory [24]. The discovery of neurons that represent various spatial features (place cells, head direction cells, border cells, and grid cells) has indicated that the hippocampus and its related areas such as medial entorhinal cortex support spatial navigation. [Giocomo \(2018\)](#) discusses recent finding suggesting that the role of hippocampus may exceed beyond spatial navigation. These studies have found hippocampal neurons representing beyond the current spatial location including past and future spatial locations, and time elapsed from a certain event. Furthermore, hippocampal neurons are heterogeneous not only in their response properties but in their connectivity, intrinsic properties and gene expressions. [Giocomo \(2018\)](#) points out that further theoretical and experimental development integrating the heterogeneity of neurons is needed toward understanding how neural representations in hippocampus are generated, and how they support memory or behavior.

Emotional processing

Emotion may influence a multitude of processes ranging from sensory perception/attention to decision-making to the execution of motor outputs. Because it is impossible to measure the subjective emotional state of animals, researchers rely on the measurement of motivated behaviors as a proxy for internal emotional state.

Emotions have been theorized to mediate the rapid selection of an appropriate behavioral response (e.g. approach or avoidance) to environmental stimuli associated with rewards or threats, the most primitive form of decision-making [25–27]. Given the critical importance of the ability to imbue environmental stimuli with positive or negative valence, amygdala circuits are well-conserved across evolution [28].

As suggested by classic experiments from the 1960s from Schachter and Singer, salient or arousing stimuli will then be assigned a positive or negative valence through associative learning processes [29]. [O’Neill, Gore and Salzman \(2018\)](#) synthesize the recent proliferation of electrophysiological, anatomical and genetic studies investigating the process of valence assignment in amygdala circuitry. As mentioned above, [Johansen and Ozawa \(2018\)](#) discuss the concept of aversive prediction error and describe recent work elucidating the underlying circuitry connecting the lateral amygdala, central amygdala and periaqueductal gray.

The central amygdala (CeA) has been described as ‘striatal-like,’ given that it receives input from the ‘cortical-like’ basolateral amygdala complex (BLA), and is composed of GABAergic medium spiny neurons [30–32]. Research in the CeA in the past few decades has emphasized aversive and defensive-related behaviors, recent work using optogenetic manipulations of different cell populations of the CeA have yielded opposing results. Fadok, Markovic, Tovote and Luthi (2018) review, discuss and reconcile these apparently contradicting results to formulate several conceptual models for the function of CeA circuits. They describe a working model for CeA function and how it has evolved with new evidence from a relay station to a gating model and come to an integrative model where the CeA integrates information about internal state and external cues and contexts to drive adaptive behavior.

The medial prefrontal cortex (mPFC), which is reciprocally connected with the amygdala [33,34], has been implicated in a wide array of functions, including both emotional regulation and social behavior [35–37]. Grunfeld and Likhtik (2018) frame work emerging largely from rodent studies on fear conditioning and extinction, anxiety, and action selection in the context of a conceptual model of mixed selectivity based on data from primate studies [38]. They focus on the contribution of input arising from the ventral hippocampus (vHPC) and BLA, as the mPFC, vHPC and BLA form the ‘emotional triad’ (a term coined by Joshua Gordon, personal communication). Based on functional and anatomical data, they outline a model for the PFC in a ‘winner-take-all’ model wherein selecting one motoric action inhibits another.

Social behavior

The concept of mixed selectivity describes the functional flexibility of PFC neurons to change their selective responding to stimuli depending on the context in a well-controlled behavioral task [38]. However, this principle may also extend itself to innate, naturalistic behaviors including hierarchy formation, aggression, and parental behavior. Zhou, Sandi and Hu (2018) explore mPFC function in the context of social hierarchy and review the assays used to quantify social rank, which will facilitate our investigation of the underlying neural mechanisms of social rank representation. Aggressive behavior may serve to establish dominance, and Aleyasin, Flanigan, and Russo (2018) explore the motivation for aggressive behavior. Aggressive behavior has been linked to activation in a wide range of circuits ranging from PFC to hypothalamic, limbic and brainstem regions, including striatal circuits traditionally associated with reward. There is some overlap between aggressive behavior and parental behavior, including activity in the medial preoptic area (mPOA), the paraventricular hypothalamic nucleus (PVN), and dorsal raphe nucleus (DRN).

To take these basic insights to translation, we must first consider the importance of studying sex differences. Neuropsychiatric diseases often show distinct prevalence in men and women, making the investigation of sex differences in animal models paramount. Here, Shansky (2018) describes changes in the field of sex differences research, and common interpretational pitfalls and potential solutions. Bredebold and Veenema (2018) discuss the role of oxytocin and vasopressin in modulating anxiety-related and social behaviors. Indeed, some innate behaviors are explicitly sex-specific, including parental behavior. Kohl and Dulac (2018) review recent advances applying circuit dissection approaches to pin down the distinct facets of parenting behavior to specific circuit components.

Reverse translation

Finally, the authors summarize work that takes a reverse translational angle to provide a mechanistic understanding for the remarkable effects of deep brain stimulation (DBS). By using genetically-encodable optogenetic tools for manipulation, Post and Warden (2018) take a reverse translational perspective in reviewing this recent work from electrical DBS of the subgenual cingulate in humans [39] with optogenetic DBS in the mouse homolog, the vmPFC. Creed (2018) draws from similar principles but discusses the application of optogenetic DBS in the context of addiction, highlighting the importance for further developing noninvasive strategies for manipulating circuit components.

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