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Current Opinion in Neurobiology

Editorial overview: Neurobiology of behavior

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Current Opinion in Neurobiology 2018, **49**:xx–yy

https://doi.org/10.1016/j.conb.2018.02.019

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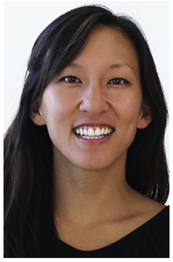

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Kay M Tye is an Associate Professor in the Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT. Her laboratory utilizes an interdisciplinary approach to functionally dissect neural circuits encoding emotional 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

Please cite this article in press as: Tye KM, Uchida N: Editorial overview: Neurobiology of behavior, Curr Opin Neurobiol (2018), https://doi.org/10.1016/j.conb.2018.02.019

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Naoshige Uchida is a professor at the Center for Brain Science and Department of Molecular and Cellular Biology at Harvard University. He received his Ph.D. from Kyoto University in Japan, where he worked on the molecular mechanism of synaptic adhesions in Masatoshi Takeichi's laboratory. He first began studying olfactory coding in Kensaku Mori's laboratory at the Brain Science Institute, RIKEN, Japan. He then joined Zachary F. Mainen's laboratory at Cold Spring Harbor Laboratory, New York, where he developed psychophysical olfactory decision tasks in rodents. He started his laboratory at Harvard University in 2006. His current research focuses on the neurobiology of decision-making and reinforcement learning, including neural computation in the midbrain dopamine system, functions of the cortico-basal ganglia circuit, foraging decisions and motor learning. His research combines quantitative rodent behaviors with multi-neuronal recordings, two-photon microscopy, computational modeling, and modern tools such as optogenetics and viral neural circuit tracing.

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

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