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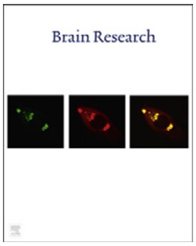

Research Report

Using optogenetics to study habits

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ABSTRACT

It is now well documented that optogenetics brings to neuroscience a long sought-after foothold to study the causal role of millisecond-scale activity of genetically or anatomically defined populations of neurons. Progress is rapid, and, as evidenced by the work collected in this Special Issue, the possibilities of what can now be done are almost dizzying. Even for those concerned with complex phenomena, such as behavioral habits and flexibility, signs are that we could be on the threshold of a leap in scientific understanding. Here. we note this special time in neuroscience by the example of our use of optogenetics to study habitual behavior. We present a basic sketch of the neural circuitry of habitual behavior built mainly on findings from experiments in which lesion and drug microinjection techniques were employed in combination with sophisticated behavioral analysis. We then outline the types of questions that now can be approached through the use of optogenetic approaches, and, as an example, we summarize the results of a recent study of ours in which we took this approach to probe the neural basis of habit formation. With optogenetic methods, we were able to demonstrate that a small site in the medial prefrontal cortex can control habits on-line during their execution, and we were able to control new habits when they competed with prior ones. The nearly immediate effect of disabling this site optogenetically suggests the existence of a mechanism for moment-to-moment monitoring of behaviors that long have been thought to be almost automatic and reflexive. This example highlights the kind of new knowledge that can be gained by the carefully timed use of optogenetic tools.

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1. Introduction

William James (1899) wrote that, “Ninety-nine hundredths or, possibly, nine hundred and ninety-nine thousandths of our activity is purely automatic and habitual, from our rising in the morning to our lying down each night”. Some might think that this view overstates the presence of habits, given modern definitions of habitual behavior. Yet, at the heart of the statement lies truth: habits, rituals and routines are pervasive, powerful and familiar parts of our lives, and have been points of great scientific interest for over a century. Now, work on the neural basis of habit formation has given us a blueprint for the brain circuits that are engaged as habits arise, and the beginnings of an idea of how they are represented in activity patterns. This work has proven critical to the study we review here, in which we took advantage of optogenetic approaches to evaluate the on-line mechanisms for habits (Smith et al., 2012). The fine temporal resolution, gene-based targeting strategies, and repeatability of optogenetic manipulations gives the opportunity to intervene

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causally in the brain's activity at a millisecond level and with cell-type specificity (Bernstein and Boyden, 2011; Fenno et al., 2011). It is now possible to address long-standing questions about when during learning and performance habits are selected and controlled and which neural circuits are necessary and sufficient for habits to be acquired and expressed. In addition, classic ideas about habits can be probed by repeating manipulations over time, including the idea that habits, once deeply engrained, can almost never be totally forgotten (Pavlov, 1927). Our first work with optogenetic methods touches on these issues, but especially, along with related work on the neural basis of addiction, underscores the potential of optogenetic approaches to this field.

2. Habits: brain substrates and conceptual frameworks

A major substrate for habitual behavior is known to depend on basal ganglia-related circuits with key nodes in the sensorimotor region of the striatum (the dorsolateral striatum, typically abbreviated as DLS). This region is a central component of circuits critical for building representations of sequences of often repeated behavior, whether learned or innate, into action patterns (Aldridge et al., 2004; Brainard and Doupe, 2002; Carelli et al., 1997; Fee and Goldberg, 2011; Graybiel, 2008; Hikosaka and Isoda, 2010; Poldrack et al., 2005; Yin et al., 2009). Such action-sequencing is adversely affected in neurologic disorders such as Parkinson's disease, for which initiating, conducting, and ending even simple sequences of movement become challenging. In other disorders, including those related to obsessive- compulsive disorder, sequences of behavior are excessively repeated. Dysfunctions in the basal ganglia appear to underlie many aspects of these conditions.

An important conceptual advance in the field was to provide conditions under which such action-sequences could be understood as habits. Even though habits are expressed as fast and sometimes skilled action-sequences, such action-sequences are not necessarily habitual. Learning theory suggests that habits emerge from a change in covert strategy alongside the observable, overt refining of behaviors that occurs as they are repeated. For example, navigational behaviors dependent on reinforced action learning can be driven by habitual response plans (e.g., run straight then turn left) or, instead, can be triggered by external cues (e.g., approach that wall, approach that food dish) (Packard, 2009; Tolman et al., 1947). A simple test has been designed to pit these two alternatives against one another by rotating the task apparatus 90-degrees after a learning phase, without moving the cues, and then determining whether an animal follows the cues or emits the learned response (McDonald and White, 1993; Packard and McGaugh, 1996; Tolman et al., 1947). A response-based (egocentric) strategy is thought to represent an ingrained habitual form of behavior, as it is fully dissociated from Pavlovian cue approach or related stimulus-directed behaviors, and can emerge as a dominant strategy with repeated running or can be instantiated early if task conditions require it (Packard, 2009).

A similar distinction in the underlying behavioral strategy comes from associative learning frameworks of habitual and goal-directed action (Balleine and Dickinson, 1998; Dickinson, 1985; Hull, 1943; Thorndike, 1898). By these accounts, habits are driven by learned stimulus–response associations, and they can be distinguished from behavior based on learned action-outcome associations. A particular behavior – say, pressing a lever – can be driven by either of these two very different underlying processes, and yet appear identical or nearly so. Which of these learning rules is being used to perform behavior can be determined, for example, through manipulations of the learned outcome value. Behavior based on action-outcome associations is sensitive to this manipulation (i.e., is goal-directed), whereas behavior rooted in stimulus–response links is reflexive and insensitive (i.e., is habitual) (Adams, 1982; Balleine and Dickinson, 1998; Dickinson, 1985; Yin and Knowlton, 2006). This differentiation made by psychologists has influenced contemporary computational models of learning and behavior, notably the analogous proposal that the brain contains separate learning systems specialized for purposeful behavior based on predictions derived from a model of the task environment (i.e., model-based) or behavior based on history and the state-dependent values of behavior that have been stored (i.e., model-free, analogous to habits) (Bornstein and Daw, 2011; Daw et al., 2005a, 2005b).

In neurobiology, studies based on these frameworks implicate the DLS and associated basal ganglia-related circuits as important not only for the performance of sequential behaviors, but also for behaviors that are outcome-insensitive and response-based (Packard, 2009; Yin et al., 2004). Additional regions promoting habits have been identified, and, with the DLS, they are thought to form parts of functional networks (Faure et al., 2005; Lingawi and Balleine, 2012; Nelson and Killcross, 2006; Wang et al., 2011; Yin and Knowlton, 2006). These networks contrast with others including the dorsomedial, associative, striatum (DMS) and limbic circuitry, which are thought to promote behavioral flexibility, outcome-sensitivity, and the use of external cues to guide behavior (Balleine and O'Doherty, 2010; Packard, 2009; Ragozzino, 2007; Yin and Knowlton, 2006).

3. Mechanisms for the shift from flexible behavior to habits

Habit formation is a dynamic process. Many habits emerge out of initial exploration of environments, learning of responses, and sculpting of purposeful action plans. With repetition, behaviors then grow less flexible and more ingrained, becoming almost reflexive. Habit formation of this sort is thought to involve plasticity not only in habit-promoting sites, but also in flexibility-promoting sites. In this way, habits might entail a tip in the balance between competing neural systems (Balleine et al., 2009; Daw et al., 2005a; Packard, 2009; Thorn et al., 2010; Yin and Knowlton, 2006). Human brain imaging studies, with the work of the Passingham group as an early example (Jueptner et al., 1997a; Jueptner et al., 1997b), as well as many other studies (Balleine and O'Doherty, 2010; Hikosaka et al., 2002; Poldrack et al., 2005; Graybiel, 2008), have shown changes in neural activity that coincide with this dynamic process, generally form anterior prefrontal to posterior frontal cortical

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