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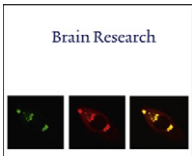

Review

Optogenetic dissection of neural circuits underlying emotional valence and motivated behaviors

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ABSTRACT

The neural circuits underlying emotional valence and motivated behaviors are several synapses away from both defined sensory inputs and quantifiable motor outputs. Electrophysiology has provided us with a suitable means for observing neural activity during behavior, but methods for controlling activity for the purpose of studying motivated behaviors have been inadequate: electrical stimulation lacks cellular specificity and pharmacological manipulation lacks temporal resolution. The recent emergence of optogenetic tools provides a new means for establishing causal relationships between neural activity and behavior. Optogenetics, the use of genetically-encodable light-activated proteins, permits the modulation of specific neural circuit elements with millisecond precision. The ability to control individual cell types, and even projections between distal regions, allows us to investigate functional connectivity in a causal manner. The greatest consequence of controlling neural activity with finer precision has been the characterization of individual neural circuits within anatomical brain regions as defined functional units. Within the mesolimbic dopamine system, optogenetics has helped separate subsets of dopamine neurons with distinct functions for reward, aversion and salience processing, elucidated GABA neuronal effects on behavior, and characterized connectivity with forebrain and cortical structures. Within the striatum, optogenetics has confirmed the opposing relationship between direct and indirect pathway medium spiny neurons (MSNs), in addition to characterizing the inhibition of MSNs by cholinergic interneurons. Within the hypothalamus, optogenetics has helped overcome the heterogeneity in neuronal cell-type and revealed distinct circuits mediating aggression and feeding. Within the amygdala, optogenetics has allowed the study of intra-amygdala microcircuitry as well as interconnections with distal regions involved in fear and anxiety. In this review, we will present the body of optogenetic studies that has significantly enhanced our understanding of emotional valence and motivated behaviors.

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1. Introduction

If evolution were a game, the objective would be to spread your genes to as many surviving offspring as possible (Darwin, 1909). The strategy would be straightforward: take actions that will support, and avoid actions that will threaten, the survival of you or your descendants. The challenges are (1) fierce competition and (2) an ever-changing environment overflowing with both familiar and novel sensory stimuli. To be competitive, you must filter out unimportant information, identifying whether certain cues are likely to have a positive or negative impact on your objective and subsequently select an appropriate behavioral response. To win, you must do this quickly and accurately.

Evolution has produced many winning designs, but all of these designs share the critical ability to differentiate between good and bad stimuli (Tooby and Cosmides, 1990). Emotions have been hypothesized to be a biological strategy for rapidly integrating previously recorded data (weighted for significance), assigning a motivational value to the stimulus, and orchestrating an appropriate behavioral response (Cosmides and Tooby, 1987; Barkow et al., 1995). In vertebrates, particularly mammals, the neural circuits thought to be important for this ability are remarkably well-conserved (MacLean, 1990). However, the precise neural mechanisms underlying the differentiation between positive and negative emotional valence are still poorly understood.

Despite the importance of understanding valence processing, technical, experimental, and practical obstacles have impeded progress in this field. First, for the field of behavioral neuroscience, studying sensory and motor systems (more amenable to discrete inputs and outputs) may have been a logical prerequisite. Second, regions involved in emotional valence processing are comprised of many different cell-types with heterogeneous functional roles that are not spatially segregated from each other within these “primitive” subcortical structures. Indeed, many regions such as the amygdala (LeDoux, 2000; Paton et al., 2006; Tye et al., 2008; Shabel and Janak, 2009; Pape and Pare, 2010), ventral tegmental area (Wise and Rompre, 1989; Schultz, 1998; Tan et al., 2012; van Zessen et al., 2012), and hypothalamus (Atasoy et al., 2012; Harris and Aston-Jones, 2006; Aponte et al., 2011; Lin et al., 2011) have been implicated in both positive and negative valence processing. This organization makes classical techniques that involve spatially-defined manipulations alone difficult to interpret on a mechanistic level. Third, valence processing involves a spatially distributed network and a multitude of parallel circuits, which demands projection-specific circuit-level control for functional dissection (Fig. 1). The indispensable nature of these functions may have led to the diffuse spatial distribution and system redundancy, which provide an evolutionary advantage in the face of accidents or injuries.

Optogenetic tools that allow for cell-type (Boyden et al., 2005; Zhang et al., 2007; Atasoy et al., 2008) and even projection-specific (Tye et al., 2011; Stuber et al., 2011) manipulation of neural activity with precise temporal control have given us the ability to overcome many of these obstacles. Although emotions are difficult to quantify, motivated behaviors provide a measurable output that summarizes many factors, including emotional state. Optogenetic tools have accelerated our understanding of a vast array of neural phenomena (Tye and Deisseroth, 2012). Here, we focus on the burst of recent insights towards understanding the neural circuits encoding emotional valence and motivated behaviors.