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Natural Neural Projection Dynamics Underlying Social Behavior

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SUMMARY

Social interaction is a complex behavior essential for many species and is impaired in major neuropsychiatric disorders. Pharmacological studies have implicated certain neurotransmitter systems in social behavior, but circuit-level understanding of endogenous neural activity during social interaction is lacking. We therefore developed and applied a new methodology, termed fiber photometry, to optically record natural neural activity in genetically and connectivity-defined projections to elucidate the real-time role of specified pathways in mammalian behavior. Fiber photometry revealed that activity dynamics of a ventral tegmental area (VTA)-to-nucleus accumbens (NAc) projection could encode and predict key features of social, but not novel object, interaction. Consistent with this observation, optogenetic control of cells specifically contributing to this projection was sufficient to modulate social behavior, which was mediated by type 1 dopamine receptor signaling downstream in the NAc. Direct observation of deep projection-specific activity in this way captures a fundamental and previously inaccessible dimension of mammalian circuit dynamics.

INTRODUCTION

Impaired social interaction is a hallmark of several psychiatric disorders, including autism, schizophrenia, depression, and social anxiety disorder. In rodents, most studies on social behavior have focused on socio-sexual behaviors, such as pair bonding and behaviors related to sexual competition (Aragona et al., 2006; Curtis and Wang, 2005; Gingrich et al., 2000; Leypold et al., 2002; Liu and Wang, 2003; Young et al., 2001; Young and Wang, 2004). However, comparatively little is known about neural circuitry regulating adult same-sex, nonaggressive social interaction, which is of potential relevance for understanding circuits that go awry in social-function disorders (Silva and Ehninger, 2009).

Pioneering studies have implicated the neuromodulator dopamine (DA) in same-sex affiliative interactions (Puglisi-Allegra and Cabib, 1997; Robinson et al., 2002; Robinson et al., 2011). DA neurons in the VTA are involved in processing emotionally salient stimuli of both positive and negative valence. The VTA is a heterogeneous region comprised of diverse cell types that may play distinct roles in modulating reward and aversion based on connectivity to different upstream and downstream structures (Brischoux et al., 2009; Budygin et al., 2012; Chaudhury et al., 2013; Kalivas and Nakamura, 1999; Lammel et al., 2011, 2012; Mirenowicz and Schultz, 1996; Tye et al., 2013). These cells project broadly throughout the brain to limbic regions such as the medial prefrontal cortex (mPFC), NAc, and amygdala, structures that may mediate both appetitive and aversive processes. However, it is unknown which if any of these projections might play a causal role in driving or inhibiting social behaviors. Moreover, in general, the real-time neural circuit dynamics causally involved in social behavior remain poorly understood, and the large number of downstream VTA targets and postsynaptic DA receptors together point to the need for new tools that allow observation of targeted cell types and their projections during naturalistic conditions and perturbation of activity in a downstream receptor and region-specific manner.

We approached this challenge by developing optical tools to selectively observe and control specific VTA circuit elements, projections, and downstream targets on a timescale relevant to social interaction. First, we sought to develop a recording technique sensitive enough to track real-time dynamics of genetically and topologically specified subsets of neuronal projections in freely moving mice, using novel photometric devices together with genetically encoded Ca^{2+} indicators (Akerboom et al., 2012; Chen et al., 2013) for direct in vivo measurement of a previously inaccessible variable: the coordinated activity of neuronal afferents projecting to a particular downstream target deep in the brain of a behaving mammal. We next applied this method to determine quantitative features of projection-specific dynamics during behavior to identify circuit elements predictive