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Reward magnitude tracking by neural populations in ventral striatum

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ABSTRACT

Evaluation of the magnitudes of intrinsically rewarding stimuli is essential for assigning value and guiding behavior. By combining parametric manipulation of a primary reward, medial forebrain bundle (MFB) microstimulation, with functional magnetic imaging (fMRI) in rodents, we delineated a broad network of structures activated by behaviorally characterized levels of rewarding stimulation. Correlation of psychometric behavioral measurements with fMRI response magnitudes revealed regions whose activity corresponded closely to the subjective magnitude of rewards. The largest and most reliable focus of reward magnitude tracking was observed in the shell region of the nucleus accumbens (NAc). Although the nonlinear nature of neurovascular coupling complicates interpretation of fMRI findings in precise neurophysiological terms, reward magnitude tracking was not observed in vascular compartments and could not be explained by saturation of region-specific hemodynamic responses. In addition, local pharmacological inactivation of NAc changed the profile of animals' responses to rewards of different magnitudes without altering mean reward response rates, further supporting a hypothesis that neural population activity in this region contributes to assessment of reward magnitudes.

Introduction

Animals enact behavioral strategies largely based on the amount of positive reinforcement or reward they expect to receive from competing courses of action (Doya, 2008; Kringelbach and Berridge, 2009). Rewards come to be associated with actions, as well as with environmental stimuli, and give rise to their perceived values. Associations are learned and values adjusted by comparing earned and expected rewards in each behavioral context (Sutton and Barto, 1981). When choosing from a set of options, animals will often allocate their decisions in direct proportion to the reward magnitude associated with each option; two equally rewarding options will be chosen with equal probability, and more rewarding options will be chosen more frequently (Herrnstein, 1970). A requirement in most types of reward-related behavior is therefore that animals have a way to assess rewards in at least semi-quantitative fashion. Most fundamentally, animals must be able to evaluate the magnitudes of intrinsically rewarding stimuli (primary rewards) in much the same way they evaluate sensory variables such as luminance, texture, and tone.

Neurons with firing rates dependent on reward magnitudes have been identified in the prefrontal cortex, striatum, amygdala, and dopaminergic midbrain (Schultz, 2015). Some of these neurons fire in absolute proportion to reward magnitude, immediately after delivery, but most have more complex dependence on behavioral variables, including the range of reward magnitudes presented in a task and the presence of stimuli predictive of rewards (Schultz, 2000). Dopaminergic fibers that project to the nucleus accumbens (NAc) have often been considered essential to reward processing, and are among those that signal when rewards are anticipated as well as experienced (Saddoris et al., 2015). The functional relationships among reward-

Abbreviations: Amyg, amygdala; AmygAM, anteromedial amygdala; AmygPL, posterolateral amygdala; BOLD, blood oxygenenation-level dependent; CPu, caudate-putamen; CgCx, cingulate cortex; DpMe, deep mesencephalic nuclei; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; EPI, echo planar imaging; GLM, general linear model; GP, globus pallidus; Hippo, hippocampus; LH, lateral hypothalamus; LS, lateral septal nucleus; MFB, medial forebrain bundle; NAc, nucleus accumbens; NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell; Tu, olfactory tubercle; OCx, orbital cortex; PiCx, piriform cortex; PO, preoptic area; ROI, region of interest; SCx, somatosensory cortex; SI, substantia innominata; SN, substantia nigra; Thal, thalamus; VP, ventral pallidum; vSub, ventral subiculum; VTA, ventral tegmental area

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responsive neurons in different brain regions and their relationship to broader neuronal networks remain a topic of intense interest. Because studies of reward are typically performed using electrophysiology or electrochemistry in awake, behaving animals, it is hard to isolate low-level neuronal events involved in integrating rewarding stimulus inputs from higher-level processes that presumably relate reward magnitudes to other stimuli or task components; it is also difficult to compare different brain regions or cell populations to assemble a comprehensive picture of neural tuning to rewards, analogous to maps of functional architecture obtained in sensory systems.

Neural stimulation methods permit the dissociation of reward delivery from other aspects of behavior, and could be particularly useful in defining mechanisms of reward magnitude computation. A robust, clinically-relevant, and empirically well-characterized technique involves electrical microstimulation of various brain regions, most prominently including the medial forebrain bundle (MFB) (Olds and Milner, 1954). The trade-off between the stimulation strength and duration of pulse trains required to support any given level of operant responding for MFB stimulation has led to the suggestion that action potentials triggered by the stimulation are summed by a neural integrator closely associated with the animal's assessment of reward magnitude and consequent behavioral performance (Gallistel, 1978; Gallistel et al., 1981; Sonnenschein et al., 2003). Importantly, MFB stimulation-mediated reward has been shown to substitute for sucrose solutions in behavioral tasks (Conover and Shizgal, 1994), implying that the circuitry activated by MFB stimulation coincides in functionally relevant ways with the neural pathways required for processing naturalistic rewards. Unlike many naturalistic rewards, however, MFB stimulation reward is easily combined with high resolution noninvasive brain imaging, and has been used by ourselves and others in recent MRI studies (Krautwald et al., 2013; Lee et al., 2014).

In an effort to discern essential components of reward magnitude processing at a whole-brain level, we combined MFB stimulation reward with behavioral psychophysics, local pharmacological inactivation, and functional magnetic resonance imaging (fMRI) in rats. This combined approach allowed us to manipulate the reward system and record quantitative neurophysiological information from distributed neural populations. We were able to survey the entire brain for foci of reward magnitude tracking—areas whose fMRI signals track psychometric reward magnitude measurements—which could then be probed with targeted brain inactivation to test whether spatially-distinct neural populations play a role in reward magnitude integration.

Methods

Implantation of stimulation electrodes and cannulae

All surgical and animal handling procedures were performed in accordance with federal and institutional guidelines, and were approved by the MIT Committee on Animal Care. Adult male Lewis rats (250–300 g) were implanted with stimulation electrodes in the medial forebrain bundle (MFB) at the level of the lateral hypothalamus (LH). Monopolar stimulating electrodes were fabricated from 0.063 mm-diameter teflon-coated silver wire (A-M Systems, Sequim, WA), cut to lengths of approximately one centimeter. These electrodes were comparable to monopolar electrodes used in previous MFB stimulation studies most relevant to our experiments, and the use of silver wire, compared with alternative materials, minimized the MRI artifact associated with magnetic susceptibility of the electrode. Approximately 0.5 mm of the insulation was stripped from one end of each electrode to form a tip. The length of the wire (63.5 mm) was threaded through 0.762/1.587 mm inner/outer (ID/OD) diameter polyetheretherketone (PEEK) tubing (McMaster-Carr, Robbinsville, NJ) and connected to one pin of a two-pin connector (Digi-Key, Thief River Falls, MN). The second pin was connected to a bare silver reference wire of 63.5 mm length and 0.125 mm diameter.

Animals were anesthetized and underwent surgery to introduce craniotomies for electrode insertion, 2.2 mm, 2.0 mm or 1.2 mm posterior to bregma and 1.7 mm left of the midline suture. Electrodes were lowered through the craniotomy to a depth of 8.6 mm below the skull surface. An additional hole was drilled through the skull for introduction of a conducting, beryllium copper screw (Antrin Enterprises, Ojai, CA); the stimulating electrode ground wire was wound around this screw and attached with silver paint. Some animals were further implanted with a 2.0 or 7.5 mm long 22 GA PEEK guide cannula (Plastics One, Roanoke, VA) for the infusion of lidocaine into NAc. Guide cannulae were fitted with a Nylon dummy cap with a stylet that protruded 0.5 mm beyond the end of the guide to prevent blockage of the cannulae. A custom-made polyetherimide head post, tapped to accept two nylon screws from the MRI coil mounting head gear, was cemented to the dorsal surface of the skull anterior to the stimulating electrode for animals undergoing fMRI. Dental cement was applied to the entire skull surface area to hold the implants rigidly in place. Electrode and cannula positions were confirmed using MRI data and histologically confirmed in a subset of rats. For several animals, electrode impedances were measured before each behavioral session using an FHC Impedance Conditioning Module (FHC Inc., Bowdoin, ME); all measured animals displayed stable electrode impedances in the range from 4.9–6.6 kΩ.

Behavioral techniques

Electrode-implanted animals underwent behavioral shaping and measurement procedures. All behavioral experiments were performed in a plexiglass operant chamber (28×21×21 cm; Lafayette Instruments, Lafayette, IN), placed in a lighted sound-proof cabinet (Med Associates, St. Albans, VT). Two infrared nose poke sensors (Med Associates) were positioned at one end of the operant chamber, 5 cm from the floor, and a light emitting diode (LED) indicator was positioned near the top of the chamber above the sensors. Input from the nose poke sensors was monitored by a laptop computer *via* a digital input/output interface (National Instruments, Austin, TX). A custom-written computer program was used to time output stimuli dependent on the detected nose pokes. Output pulses from the computer were used to trigger cathodal stimulus pulses (0.2 ms) delivered at frequencies from 44–386 Hz by a constant current isolated stimulator (World Precision Instruments Isostim A320R, Sarasota, FL). The applied frequencies are in the standard range used to evoke MFB stimulation reward-related behavioral effects in animals, and are also comparable to clinically relevant deep brain electrical stimulation frequencies, which are typically delivered at over 100 Hz. Poles of the stimulator were shorted to one another in between stimulus pulses to prevent charge buildup on the electrodes, and pulses were visualized on an oscilloscope to verify consistent amplitude and pulse shape.

Animals were initially shaped to perform nose pokes to elicit MFB stimulation. In a typical experiment, an animal was rewarded for each nose poke with a one second 150 Hz train of 0.2 ms pulses, delivered at the maximum stimulus current (0.3–0.9 mA) for which no overt motor artifact was observed. The minimum interstimulus interval was 0.5 s. Shaping sessions lasted 30 min to one hour, once per day, for 2–10 days. Animals that displayed fewer than ~20 nose pokes per minute were eliminated from the study. Following shaping, psychometric "reward titration" curves were measured using a two choice operant task. The experimental procedure was based on studies of Gallistel and others (Gallistel and Leon, 1991; Mark and Gallistel, 1993; Simmons and Gallistel, 1994), who have shown that rats prefer rewarding stimuli of increasing intensity, up to a saturation point beyond which more intense stimulation is indistinguishable from the saturating reward.

Rats destined for imaging experiments were placed in an operant chamber with two nose poke sensors, and their behavior was monitored over a series of five-minute trials. Triggering of either sensor during a trial elicited a 1 s pulse train (0.2 ms pulses) of MFB