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Dopamine and Reward: Comment on Hernandez et al. (2006)

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Many lines of evidence suggest that the dopaminergic projection from the midbrain tegmentum to the forebrain must play a critical role in mediating the behavioral effects of natural and artificial rewards, with brain stimulation reward and addictive drugs included in the latter category. However, a closer look reveals many incongruities. The work of G. Hernandez et al. (2006) resolves several puzzles. It implies that the dopaminergic projection does not carry the signal that encodes the magnitude of a brain stimulation reward. It suggests that the elevation in the tonic levels of dopamine consequent on brain stimulation reward modulates the registration of the magnitude of the reward. This reconciles the psychophysical evidence with the pharmacological, electrophysiological, and anatomical evidence. However, some serious puzzles do remain.

Keywords: dopaminergic projection, reward, reinforcement learning, medial forebrain bundle

Behavioral neuroscience attempts what philosophers of science call "material reduction," to distinguish it from "analytic reduction." It attempts to establish the cellular and molecular identity of mechanisms and processes whose existence and properties have been inferred from behavioral observations. Working in the other direction, it attempts to assign a behavioral function to the neural systems revealed by anatomical and electrophysiological analysis. The task is immensely difficult. We get scraps of evidence from many different techniques, but, as in the early pages of a mystery novel, the clues seem to point in different directions. It is hard to find a story that accounts for all of the seemingly relevant observations, so behavioral neuroscientists often fall back on the maximally noncommital claim that a neural system or mechanism is "involved in" some behavioral phenomenon. The difficulties encountered are well illustrated by the intertwined attempts to move in both directions by establishing the neural basis of reward while also assigning a behavioral function to the dopaminergic projections from the ventral tegmentum to the forebrain. The ingenious and technically demanding experiments by Hernandez et al. (2006), in this issue, make an important contribution to both efforts.

That the two efforts must somehow converge has long seemed likely because of the first-order congruence between several lines of evidence. First, there is the evidence from behavioral pharmacology that blockade of the D_2 receptor blocks the rewarding effects of natural rewards, of electrical stimulation of the medial forebrain bundle, and of addictive drugs (Elmer et al., 2002; Gallistel & Davis, 1983; Gallistel & Freyd, 1987; Wassermann, Gomita, & Gallistel, 1982; Wise, 2002, 2004; Wise & Rompré, 1989). Second, the dopaminergic projection from the midbrain to the forebrain is one (among many) components of the medial forebrain, which is the principal locus for diencephalic electrode placements that produce a rewarding behavioral effect (Forgie & Shizgal, 1993; Olds, 1976). It is also the system that is most strongly and clearly metabolically activated by rewarding stimulation at sites along the bundle (Gallistel, Gomita, Yadin, & Campbell, 1985; Simmons, Ackermann, & Gallistel, 1998). Third, there is the electrophysiological evidence that dopamine firing is sensitive to the predictability of rewarding events (Fiorillo, Tobler, & Schultz, 2003; Schultz & Dickinson, 2000; Schultz et al., 1995) in ways that make interesting connections to contemporary theories of reinforcement learning (Daw & Touretzky, 2002; Montague, Dayan, & Sejnowski, 1996). Finally, there is the evidence from voltametry that stimulating at reward sites in the ventral tegmentum, where the projection originates, releases dopamine in the nucleus accumbens, which is a major terminus of the projection (Fiorino, Coury, Fibiger, & Phillips, 1993). As stories go in behavioral neuroscience, those diverse but converging lines seem to make a good one.

With a closer look, however, perplexities emerge. Many of them arise from work that exploits one of the great advantages of brain stimulation reward, the ability to do psychophysical experiments to determine from the behavior itself quantitative cellular level properties of its neural substrate (Gallistel, Shizgal, & Yeomans, 1981; Miliaressis, Durivage, & Rompré, 1982; Murray & Shizgal, 1996; Shizgal, 1989, 1997; Yeomans, 1988). This makes it possible to compare the electrophysiologically or voltametrically measured properties of a neural system to the behaviorally measured properties of the neural substrate for brain stimulation reward. Quantitative agreement between these measures would greatly strengthen the case for identifying the dopaminergic projection with the substrate for brain stimulation reward and, by implication, for natural reward. Unfortunately, the measures do not agree. The behaviorally measured refractory period, conduction velocity, and direction of conduction of the neural substrate for the rewarding effect are not those of the dopamine neurons (Shizgal & Murray, 1989). This implies that the ascending dopaminergic projection system is not the system whose *direct* excitation by electrodes in the medial forebrain bundle eventuates in a rewarding effect. It may be a critical indirectly (that is, trans-synaptically) excited link in the chain of neurophysiological events leading to the formation

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of an enduring memory for the magnitude of the reward (cf. Yeomans, 1995), but it cannot be the first link. This makes the anatomical congruence between rewarding electrode sites and the dopaminergic projection a coincidence, robbing it of its evidentiary value.

Another perplexity is that the electrophysiological characteristics of dopamine neurons revealed by single-unit recording in monkeys responding for natural rewards do not seem consistent with the hypothesis that the dopamine neurons carry the rewarding signal in brain stimulation reward. In the monkey, dopamine neurons do not fire in response to an expected reward only in response to an unexpected or uncertain one, and, most distressingly, to the omission of an expected one (Fiorillo et al., 2003). In the brain stimulation experiments, the rats presumably expect the rewarding effect of each train, which always comes immediately after they depress the lever. Their behavior depends on the repeated confirmation of this expectation, because it ceases very soon after the lever is disconnected from the stimulator.

There are also problems with the voltametric evidence: The voltametrically measured transient releases of dopamine triggered by rewarding stimulation of the medial forebrain bundle decline to unmeasurable levels within half an hour, while the self-stimulation behavior continues with undiminished vigor (Fiorillo et al., 2003; Kilpatrick, Rooney, Michael, & Wightman, 2000). Moreover, combinations of stimulating pulse duration and pulse current that yield equivalent rewarding effects do not yield equivalent levels of dopamine release (Miliaressis, Emond, & Merali, 1991).

The Hernandez et al. (2006) work resolves some of the perplexities, and, gratifyingly, for once the psychophysical measurements are congruent with the physiological measurements. They show that, unlike the transient dopamine releases, tonic levels of dopamine are elevated throughout prolonged periods of rewarding stimulation and that when the stimulation is dense, the eventual reduction in these elevated tonic levels is accompanied by a reduction in the psychophysically measured rewarding effect. The effects on both tonic dopamine levels and the behaviorally measured efficacy of brain stimulation reward are the same regardless of whether the prolonged stimulation is predictable. This result implies that the dopamine fibers do not carry the rewarding signal itself. Rather, tonic levels of dopamine, presumably resulting from tonic elevation in the firing of dopamine neurons during periods when rewards are received, modulate the registration of the rewarding effect of a transient signal presumably carried by a different projection. The further implication is that D_2 antagonists block the rewarding effect by removing a tonic enabling signal rather than by blocking the transmission of the neural signal that encodes the magnitude of the rewarding signal produced by a single brief train of stimulation. This removes the need to reconcile the Schultz et al. (1995) findings with the brain-stimulation/reward findings, because it implies that the kind of transient activity they analyzed is not the activity that encodes the magnitude of a brain stimulation reward.

Perplexities remain, however. Probably the most vexing is the conundrum of why even very large lesions of the medial forebrain bundle often have very little effect on the psychophysically measured magnitude of the reward (Gallistel, Leon, Lim, Sim, & Waraczynski, 1996; Simmons et al., 1998; Waraczynski, 1988). This poses an anatomical mystery of the first order.

Another perplexity concerns the conceptual framework required to understand the different time scales on which the dopaminergic projections appear to operate (cf. Schultz, 2002). How do the transient signals seen in these neurons when an unexpected reward or nonreward occurs relate to the rewarding effect of a brief train of pulses delivered to the medial forebrain bundle?

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