Dopamine: Don't Underestimate the Force

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Dopamine is implicated in reward processing and movement. A new study describes an unexpectedly tight relationship between dopamine activity and the forwards and backwards forces an animal exerts in response to rewards, suggesting a potential reconciliation of these two roles.

"Nothing happens until something moves"
Albert Einstein

Research into the function of dopamine over recent decades has been fortunate to be able to build upon two foundational pillars. First, it has long been known that the loss of dopamine neurons in disorders such as Parkinson's disease causes severe motor impairments [1]. Second, it is now well established that the activity of many midbrain dopamine neurons, and dopamine release in parts of the striatum, correlates precisely with a reward prediction error (RPE) derived from reinforcement learning models, signalling the discrepancy in value between expected and actual events to enable reward learning to occur [2]. However, a key, and enduring, question that has faced the field is how this single molecule, transmitted widely across large areas of the brain, could underpin these two seemingly distinct functions. Is it the case that there are distinct populations of dopamine neurons, or timescales of activity, for signalling RPEs and triggering movements or might there instead still be a unifying framework that formally captures the relationship of dopamine activity to both? In the current issue of *Current Biology*, Hughes, Bakhurin and colleagues present intriguing new results to support the idea that the activity of ventral tegmental area (VTA) dopamine neurons *can* be captured by a shared variable: the animal's impulse vector, or the forwards and backwards forces it exerts over time [3].

For many years, the most quantitatively precise association between dopamine activity and external events has been described in relation to reward-predicting cues and rewards

[4]. Indeed, in lateral parts of the VTA, nearly every identified dopamine cell was reported to compute an RPE [5]. By comparison, any relationships with motor behaviour appeared weaker and more inconsistent [6]. Recently, however, several elegant studies in mice recording activity from identified dopaminergic cell bodies or axons while closely monitoring their movements have reported significant rapid modulations of dopamine activity around the initiation of spontaneous movements [7-11]. These could occur even in the absence of any overt reward [8,9]. Importantly, there was a large degree of separation between those active prior to movement and those responding to reward [7,9]. This separation is partly tied to the location of cell bodies in the midbrain, with average increases in activity in dopamine axons from the substantia nigra pars compacta more strongly aligned with the start of locomotion and the VTA more with reward [7]. An accumulation of such findings has led some prominent researchers to question the long-held premise that there might be a common algorithm to describe dopamine function [6], a perspective that appeared supported by recent work showing a diversity of variables encoded across populations of dopamine neurons [12].

One major difficulty in distinguishing when dopamine is encoding movement and when it is signalling rewards is that actions are often taken to improve an animal's state and rewards in turn often prompt actions to obtain them (Figure 1). In fact, when reward-predicting cues and the reward-seeking actions that follow are dissociated, either by the animals' slower reaction times on a subset of trials or by experimental design, dopamine levels measured in the nucleus accumbens were found to be modulated by action initiation as well as the potential rewards on offer [13,14]. It might seem that using head-restrained animals to facilitate challenging recording techniques might simplify the problem. However, restraining an animal neither prevents them from trying to move nor from engaging in a whole host of other movements. With this in mind, a number of recent studies, including by the authors here, have begun to level a finer-grained analysis upon movement during reward based tasks, using video tracking, force sensors and accelerometers to relate measurements and manipulations of cell activity to postural changes and action [10,15].

In this vein, Hughes, Bakhurin and colleagues employed "orthogonal sensors" to enable precise measurement of the forces produced in different directions as mice received regular deliveries of rewards on a fixed time schedule [3]. By combining this with electrophysiological recordings, some using optogenetic identification to distinguish dopamine from non-dopamine containing neurons, they were able to identify three classes of VTA dopamine neurons with firing patterns tightly correlated to force production: *Fast Backward* neurons, which increased their firing rates with the production of backwards force and decreased them with the production of forward force; and *Fast Forward* and *Slow Forward* neurons, which have opponent firing rates to fast backward neurons, on fast (subsecond) and slow (several second) timescales respectively. Each population of neurons show an astonishingly tight linear correlation with the impulse vector - the integral of force produced over time. Furthermore, rather than simply providing a readout of directional force, manipulations of VTA dopamine activity using optogenetics showed a causal relationship with force production; VTA stimulation produced forward force proportional to the pulse number (as well as eliciting anticipatory licking of the reward spout), while inhibition produced an initial exertion of backwards force followed by a rebounding forward force. The authors assert that net forward force is exactly as could be expected given that each class of force-related dopamine neurons made up roughly a third of the selective population recorded.

While there have been a few previous reports linking changes in VTA dopamine activity or release in projection targets like the nucleus accumbens to action initiation [8,10,14], this is the most comprehensive description relating VTA dopamine firing patterns to specific components of movement. The appeal of these data is that they revitalise the possibility of a common algorithm to explain a seeming heterogeneity of dopamine neuron firing patterns. What is unexpected is that this has come from the movement standpoint rather than reconciliation under a version of the RPE hypothesis.

So where does this leave RPE-based theories? The authors contend that their data cannot be explained under this framework as the reward-evoked dopamine responses were consistently observed, even though rewards are fully predicted (which should not occur if

dopamine is reporting the error in prediction). As they rightly acknowledge, the critical test will require similarly close monitoring of forces to be made during the type of tightly controlled tasks that have provided the key supporting data for RPE-like dopamine signals. It is noticeable that reward responses can be surprisingly persistent in mice performing simple Pavlovian tasks even after the animals have apparently acquired the cue-reward association [16]. One attractive facet of the impulse vector theory is that it is a clearly testable and potentially falsifiable hypothesis. If and when such experiments are performed, it would be a remarkable finding if the firing patterns of dopamine neurons shown to track RPE signals with arithmetic precision are in fact more directly reflecting the direction and vigour of the animal's movements.

Just as importantly, the question of the function of these dopamine signals, and how they coordinate with wider brain circuits, will likely remain a live question in the years ahead. For instance, in the current study and others, it is not the case that activation of dopamine neurons always causes a change in behaviour, particularly when optogenetic stimulation is titrated to mimic endogenous changes in activity; this only occurs in animals that have had some exposure to rewards in the context of a task [3,10] or are exploring an open field [9]. In one study that directly compared dopamine and noradrenergic neurons when monkeys need to exert force to gain reward, both populations increased activity prior to making a response, but it was actually only the noradrenergic cells that were positively modulated by the amount of exerted effort [17]. Moreover, in the current study, there were also some changes in force observed on the trial after optogenetic manipulation, potentially suggestive of reinforcing effects beyond the immediate trial. What defines when dopamine promotes action and when it causes learning, and what the interaction between these two functions are, will continue to be hot topics for research [10,18]. Finally, while it is computationally attractive to strive for a unifying function, it is worth remembering that several studies in Parkinson's disease patients have observed two seemingly separable influences of dopamine on reward sensitivity and motor activation [19,20].

What the current study highlights persuasively is that progress on these issues will best be made when experimenters pay close attention to the behaviours animals emit within

carefully controlled tasks - as well as the fact that interpreting a "simple" neuronal response to reward is usually anything but simple.

Declaration of Interests

GWJ is supported by a BBSRC Industrial CASE studentship awarded to MEW in collaboration with H. Lundbeck A/S (Copenhagen). The authors have no other competing interests.

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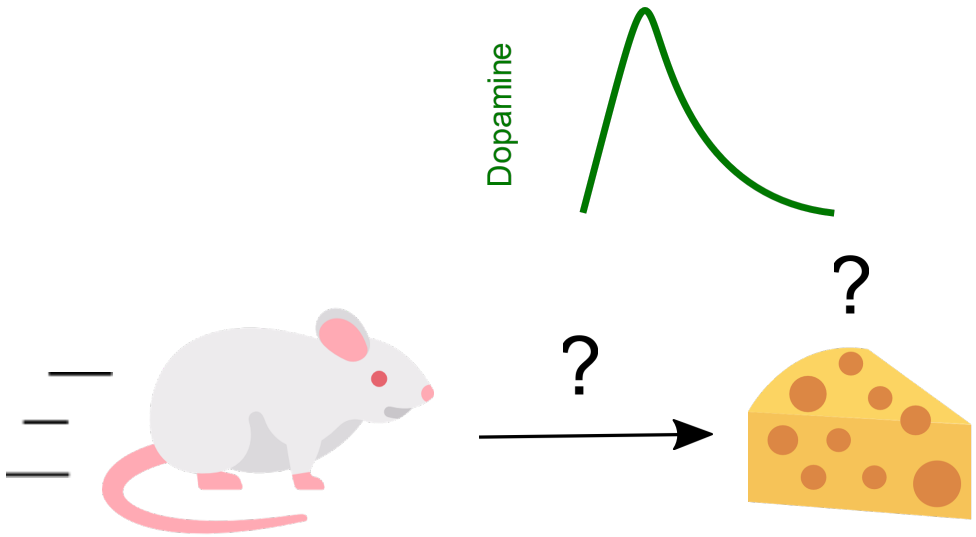
Figure 1. What is the relationship between dopamine, reward and action? It is well established that the activity of a large number of dopamine neurons, and dopamine release in many terminal regions, increases in response to uncued delivery of rewards. But given rewards tend to prompt actions to obtain them and actions are often made to improve an animal's state, can we be sure which is driving changes in dopamine? Icons by Freepik from flaticon.com.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