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Viewpoint

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Probing the Neurochemical Correlates of Motivation and Decision Making

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ABSTRACT: Online electrochemical detection techniques are the state-of-the-art for evaluating chemical communication in the brain underlying motivated behavior and decision making. In this Viewpoint, we discuss avenues for future technological development, as well as the requirement for increasingly sophisticated and interdisciplinary behavioral analysis.

KEYWORDS: *Fast-scan cyclic voltammetry, biosensors, in vivo neurochemical monitoring, reward seeking*

Appropriate motivation and adaptive decision making is crucial to survival. Identifying the chemical neurotransmission underlying such behavior is an essential component to understanding and treating motivational symptoms that are core features of addictive, binge eating, obsessive-compulsive, and depressive disorders, as well as other psychiatric conditions. Motivated behavior can be modeled in rodents trained to predict natural or drug reinforcers on the basis of environmental stimuli (Pavlovian conditioning) or their own actions (instrumental conditioning). Measuring signaling neurochemicals in rodents behaving in these models has provided important insights into the chemical communication underlying motivated behavior. However, to distinguish neurotransmitter signaling associated with discrete reward-related events, measurements must occur with high temporal resolution.

Voltammetric sensors can achieve this goal, providing real-time measurements of neurochemical concentration changes. These devices consist of implanted electrodes that detect neurochemicals present at their surfaces based upon their redox properties. Electrical currents are generated through the oxidation or reduction of molecules in response to an electrical potential. This potential may be applied to the electrode constantly or as a waveform. Thus, in addition to diffusion through the tissue, the temporal resolution is limited by electron-transfer reactions (microseconds to milliseconds) or the duty cycle of the waveform application (typically less than a second), respectively. The range of the applied potential is limited to voltages that do not produce significant electrolysis of water (i.e., the physiological electrolyte). Accordingly, "electroactive" neurochemicals are those that undergo electrolysis within these limits (e.g., biogenic amines), which are constrained practically to $\sim \pm 1$ V. To avoid generating currents large enough to depolarize or lyse cells, electrodes need to be small, typically with micrometer dimensions, which provides advantages associated with spatial resolution sufficient to restrict recordings to discrete brain nuclei.

Electrochemical applications to monitor neurotransmission during behavior have routinely been carried out in freely behaving rodents but, more recently, have been extended to nonhuman and human primates. The most commonly used electrochemical approach for monitoring neurochemistry during behavior is background-subtracted fast-scan cyclic voltammetry (FSCV) for subsecond, dopamine detection. FSCV uses a voltage waveform that offers chemical resolution to discriminate dopamine from other electroactive species by providing an electrochemical signature in the form of voltage−current information (cyclic voltammogram). Other electroactive molecules, including serotonin, norepinephrine, and adenosine, have been measured with this technique in vivo following stimulated release, and it is anticipated that in the future we will see reports on the temporal dynamics of these additional signaling molecules during behavior.

Subsecond detection of nonelectroactive neurochemicals can be achieved with the addition of a biological recognition element to the electrode. The recognition element is typically an enzyme that has substrate selectivity and generates an electroactive reporter molecule. This approach has most notably been applied to the monitoring of glutamate transmission with the enzyme glutamate oxidase coated on electrode surfaces. Glutamate oxidase catalyzes the oxidative deamination of glutamate, generating the byproduct hydrogen peroxide, which can be electrochemically detected using constant-potential amperometry. While enzyme-based biosensors use fairly selective biological recognition elements, electrodes can potentially respond to other electroactive compounds in the extracellular space, in addition to the reporter molecule. Selectivity is achieved by application of polymer layers designed to repel cationic and anionic interferents. Electroenzymatic biosensors have also been used for the detection of choline (a proxy for acetylcholine), acetylcholine, glucose, and lactate. Lastly, while microdialysis coupled to analytical measurements

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does not traditionally provide the required response time, recent technological developments have greatly improved the temporal resolution, allowing measurements on the order of seconds.

High-resolution electrochemical sensors have provided fundamental information regarding the chemical communication underlying motivated behavior. Among the many examples, dopamine release in the nucleus accumbens core has been shown to respond phasically to Pavlovian reward-predictive cues and to precede the initiation of instrumental reward-seeking actions.[1] Similarly, glutamate release in the basolateral amygdala also correlates with reward-seeking activity.[2] Reward-seeking behaviors are, however, guided by myriad psychological processes. Even a simple daily behavior like going to get lunch (or pressing a lever to earn food) can be controlled by varied and complex psychological processes. As the clock strikes noon you may cognitively consider your available lunch options, make a decision, and then execute the plan. On the way to lunch, however, environmental cues (e.g., a colleague's delicious-smelling slice of pizza) may influence your choice of meal. Of course, you may proceed to lunch without any forethought at all, merely executing your typical lunchtime habit. What then are the specific messages encoded in the chemical signals that we record during motivated behavior?

The answer to this question may lie in decades' worth of psychological evaluation of Pavlovian and instrumental conditioning in animals, mostly rodents. Unlike humans, we cannot ask a rat why it pressed a lever for food. We can, however, with appropriately designed experiments and tests probe the content of what the rat has learned and the psychological constructs guiding its behavior. By combining these behavioral experiments with high-resolution neurochemical monitoring, we can clarify the precise messages encoded in the neurochemical concentration changes detected during motivated behavior, even at the algorithmic level. In a recent example of this type of approach, the phasic release of dopamine in the nucleus accumbens core was shown to "transfer" from food-reward delivery to the Pavlovian predictors of that reward with learning, mimicking the reward-prediction error signal (i.e., discrepancy between the actual and expected value of an event) thought to mediate associative learning. Strikingly, this transition will only occur in rats for which the stimulus acquires motivational value,[3] suggesting that dopamine may serve as a teaching signal selectively for the formation of stimulus-response associative structures that rely on such value.

Coupling neurochemical analysis with informative behavioral paradigms is not always straightforward. In many tasks, the subject, rather than the experimenter, controls the timing of behavioral events, making it difficult to time lock recorded neurochemical changes with repeated behaviors for signal averaging and standard analysis (i.e., averaging across experimenter-predetermined trials). Care must be taken, however, when adjusting behavioral paradigms to fit with recording methods because even small changes in a behavioral design (e.g., adding an intertrial interval or signaling reward) can fundamentally change the balance of psychological constructs underlying the behavior. In many cases, it may be appropriate (and preferred) to adjust the method of analysis to suit the behavioral measures (for a recent example, see ref 4). In this respect, we have much to learn from computational neuroscientists who have spent considerable effort distilling the psychological processes underlying motivated behavior and decision making into mathematical models that generate clear predictions for behavior and associated neurochemical signals. High-resolution voltammetry methods afford a practical approach for testing these predictions.

Of course, when considering sophisticated behavioral analysis, there is also the challenge of recording longitudinal changes in neurotransmitter dynamics over the course of learning or with successive testing. Recent advances in chronically implantable microelectrodes[5] have been fundamental in this regard. In addition to providing longitudinal recordings from the same sampling space under the same conditions (e.g., identifying the progressive changes that take place during drug self-administration or learning), chronic recordings provide a means for within-subject comparisons of manipulations of different variables. For example, comparisons between perturbation states or systematic alterations of parameters carried out on different experimental days enhance statistical power and reduce animal use. Importantly, because electrodes do not need to be implanted prior to each behavioral session, the use of chronically implanted electrodes minimizes test-day stress, which is vital considering many behaviors of interest are highly sensitive to acute stress. Chronic recordings have yet to be fully taken advantage of with electro-enzymatic neurochemical detection and will be an important avenue for future work. While chronically implanted, fixed-location microelectrodes continue to be applied and advanced, the advantages afforded by drivable electrodes—especially the ability to optimize electrode placement for "hot" and "cool" release spots—should also be exploited to gauge spatial heterogeneity of chemical signaling in the brain. Indeed, further evaluation of within-region heterogeneity in neurotransmission, especially as it relates to motivation microcircuits, is an important avenue for future consideration. More traditional acutely implantable electrodes innately offer this feature, and chronically implanted electrode arrays with individually drivable electrodes have recently been developed.

There are many other avenues wherein online electrochemical detection technologies must be improved as we continue to use them to advance our understanding of the chemical communication underlying motivated behavior and decision making. Most obvious is the ongoing drive to improve objective performance parameters such as sensitivity, selectivity, and temporal resolution. However, it will also be important to expand our repertoire of recordable neurochemicals. Likewise, we must consider that neurochemicals work in concert to influence behavioral output and, therefore, a valuable avenue for future technical development is the development of sensors capable of simultaneously recording multiple transmitters from the same sampling space, online and in real time.

Lastly, it is imperative to acknowledge that neurochemical recording techniques provide correlational data—incredibly rich correlational data—but correlational nonetheless. Interference approaches (discussed in another Viewpoint in this issue) are required to provide a complementary causal analysis. With targeted and rapid control over specific populations of cells, optogenetic technology is a well-matched interference method to couple with high-resolution electrochemical detection. This approach can be used to selectively mimic or attenuate recorded chemical signals to test their causal role in behavior.

Despite the recent success of in vivo neurochemical monitoring, much is still unknown regarding the chemical messages that underlie motivated behavior and decision making. This information is vital to our understanding of the many disorders marked by maladaptive motivation and

behavioral control. Technological advances are needed to improve our ability to measure neurochemical communication with a high degree of physiological relevance. These should proceed in parallel with the continued application of current and emerging technologies and applied to behavioral questions generated on the basis of the long history of psychological, cognitive, and computational research.

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Notes

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