

Peer Review

Review of: "GABAergic Neurons from the Ventral Tegmental Area Represent and Regulate Force Vectors"

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This study, "GABAergic Neurons from the Ventral Tegmental Area Represent and Regulate Force Vectors," elucidates our understanding of how ventral tegmental area (VTA) GABA neurons may modulate different behaviors, particularly in relation to reward processing and force exertion. The study employs a well-designed combination of in vivo electrophysiology, optogenetics, and behavioral paradigms to provide novel insights into the function of these GABA neurons. Their main finding challenges our prevailing notion that VTA GABA neurons primarily encode reward prediction; instead, the study's results suggest that these neurons modulate performance in real time. These findings may help refine our present conceptual framework for VTA GABA-neuron function and should be of broad interest to those of us studying various aspects of reward processing, motivation, and motor control. Comments follow:

A primary strength of the study is the novelty of its major finding. Using state-of-the-art approaches, this study challenges existing models of VTA GABA neuron function by demonstrating that these GABA neurons primarily encode force exertion rather than reward prediction. This finding is in line with a growing body of literature suggesting that VTA neurons contribute to behavioral execution rather than solely encoding learning signaling. In addition, combining electrophysiology, optogenetics, and continuous force measurements provides the strong evidence necessary to support the proposed conclusions; this is especially important when their findings challenge existing models of this network.

Generally, I found the manuscript to be well-written, and the authors thoroughly contextualized their findings within existing literature, doing so by addressing potential alternative interpretations and by linking their results to broader models of VTA function, with minor caveats, see below.

My suggestions focus on the need for clarification of reward-related signals as it compares to previously published (and well-established) work. While the authors provide a convincing argument that VTA GABA neurons might not encode reward prediction, a more explicit discussion of how their findings relate to previous studies that reported reward-related activity in these neurons (e.g., Cohen et al., 2012; Eshel et al., 2015, both already cited in the manuscript) would be helpful. Presently, they indicate that their findings are unlike those of Cohen or Eshel, but it would be helpful to reconcile these differing interpretations by providing a clearer picture of how VTA GABA neurons interact with DA neurons in reward processing, beyond what is presently presented in the Discussion.

Also, the manuscript briefly acknowledges the presence of glutamatergic and glutamate-GABA co-releasing neurons in the VTA. Given the growing appreciation for the functional diversity of VTA cell types, a more detailed discussion on whether these neurons might contribute to the observed force exertion effects would be helpful and, perhaps, provide greater context for the findings reported here.

Minor suggestion: The manuscript indicates that VTA GABA neurons project widely and suggests that certain subpopulations may have stronger downstream effects than others. While the study does not directly investigate these pathways, a brief discussion of how future research could dissect the circuit mechanisms underlying these behavioral effects would be helpful, beyond describing it as simply a limitation of the study.

Again, this study provides interesting evidence that VTA GABA neurons modulate force exertion and performance rather than reward prediction. The study is methodologically strong and offers new and interesting insights that may refine or even redefine our understanding of VTA function. Addressing the points outlined above would strengthen the manuscript by clarifying its implications and positioning their findings more firmly within the broader literature on reward processing; this is especially important given the novelty of the findings and how it challenges present models.

Declarations

Potential competing interests: No potential competing interests to declare.