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Peer Review

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

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The paper presents a series of in vivo optogenetic electrophysiological and behavioral experiments addressing the information coding and behavioral role of GABAergic neurons in the VTA. The authors show the existence of 4 types of neurons that were identified on the basis of the relationship between the cells' firing rate and the direction of locomotor force exerted by mice in a head-fixed reward collection task (i.e.: direction selective forward excited or backward inhibited, direction selective backward excited or forward inhibited, and bidirectional excited or inhibited cells). Additional experiments also showed that optogenetic manipulation of GABAergic neurons in the same area influences the exerted force of the animal.

Critique.

The main concern with the study arises from three potentially related but distinct discrepancies between the presented findings and earlier results. First, it is difficult to reconcile the coding properties of bidirectional cells with the Type-II and Type-III cells of Cohen et al. 2012, and Eshel et al. 2015. In the earlier studies, although the head-fixed setup included a fixed location of the reward port, it is reasonable to assume that the mice exerted a forward force on CS+ trials and possibly also a backward force on CS-(and/or punishment) trials. If this was the case, the Type-II and III cells may correspond to the directional neurons described in this study. However, this also means that bidirectional coding would have been apparent as individual cells exhibiting excitation or inhibition by both the CS+ and the CS- trials, which was not reported there. Second, despite the use of the same transgenic mouse strains and AAV serotypes (AAV1, 5, 8), Cohen et al. 2012, and Eshel et al. 2015 specifically failed to transfect any of the Type-III neurons (CS+ inhibited cells), which corresponded to the ⅓-½ of all immunocytochemically identified (GAD67+ or VGAT+) neurons, which strongly

 doi.org/10.32388/XJTYAK

suggests that the earlier studies and the present results sampled neurons from different brain nuclei. Finally, although the location of the electrode tracts was not specifically clarified (using electrolytic lesion or other methods), the histological images shown in Fig 2A and Fig 6A suggest that at least a subset of the cells may have been sampled from the IPR. This is significant because the IPR is known to contain GABAergic neurons that encode the kinetics of locomotor behavior (e.g.: Sharp et al., 2006). Together, these 3 issues question whether the data is from the VTA and represent the properties of GABAergic neurons in this brain area. This concern is more acute because if some of the 4 cell types are not in the VTA, the publication could significantly confuse the literature on the VTA. The authors need to provide clear evidence that all 4 types of cells are from the VTA. For example, an electrolytic lesion at the end of the recording tract located inside the VTA and above/outside the IPN would clarify this concern.

Minor:

In Fig. 2A, the transfection of neurons in the IPR appears to be absent, and this is at variance with the high level of transfection of the same nucleus in Fig 6A. It would be important to clarify this discrepancy. In addition, further discussion of the behavioral results may also improve the article.

Declarations

Potential competing interests: No potential competing interests to declare.