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Cortex-wide Computations in Complex Decision Making in Mice

Pankaj K. Gupta[1,2] and Timothy H. Murphy[1,2,*]
[1]Department of Psychiatry, Kinsmen Laboratory of Neurological Research; University of British Columbia, Vancouver, BC V6T 1Z3, Canada
[2]Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC V6T 1Z3, Canada
*Correspondence: thmurphy@mail.ubc.ca
https://doi.org/10.1016/j.neuron.2019.10.043

Seemingly, a paradox exists between reports of wide-scale task-dependent cortical activity and the causal requirement for only a restricted number of motor and sensory cortical areas in some behavioral studies. In this issue of *Neuron*, Pinto et al. (2019) indicate that scenarios where mice must accumulate evidence and hold it during a delay period are causally linked to wide regions of cortex.

A cornerstone of neuroscience is the association of unique cortical areas with specific functions. While this is clear for unimodal sensory processing, work extending back to Lashley's doctrine of neuronal mass action (Lashley, 1931) posits that complex tasks are widely distributed. Lower cognitive loads can be more localized, while complex tasks are orchestrated across larger regions of brain and cortex. Recently, through the development of mouse lines expressing channelrhodopsin-2 in all GABAergic neurons (VGAT-ChR2) (Zhao et al., 2011) and the use of transcranial brain windows, reversible optical inactivation of candidate cortical regions has shed causal light on their involvement in increasingly complex behaviors. In this issue of *Neuron*, Pinto et al. (2019) contrast the role of several cortical areas during an elegant virtual reality (VR) decision-making task. They show that a complex accumulation of evidence task involves more spatially distributed cortical computations than simpler actions in mice. Previous cortical inactivation studies have found relatively localized effects on performance, even though wider areas of cortex are potentially activated by the tasks. In seminal work employing multisite cortical VGAT inactivation, Guo et al. (2014) and Chen et al. (2017) have selectively implicated the anterior lateral motor (ALM) cortex and medial motor cortex (MM) in decision/motor preparation, as well as the sensory phase of the task, by unilateral as well as bilateral (Li et al., 2016) inactivation. Guo et al. (2014) also found that vibrissal primary somatosensory cortex (vS1) was necessary for stimulus sensing. Gilad et al. (2018) made inactivations by (AAV)-CAG-ArchT-GFP, as well as VGAT-ChR2-EYFP, where they found multiple causally linked areas for stimulus sensation and memory in secondary motor cortex (M2) or lateral posterior areas (P). Interestingly, area P only had a causal role during the delay period for animals using a passive body movement strategy (Gilad et al., 2018).

While previous work indicated that sensory processing and/or memory was causally linked to selective cortical areas, the use of wide-field functional imaging indicates that the response to even brief sensory stimuli, such as whisker deflections, tones, or tactile stimuli, are distributed across wide cortical networks (Ferezou et al., 2007; Mohajerani et al., 2013).

Pinto et al. (2019) describe how the causal role of brain areas can change across similar tasks with different cognitive demands. They suggest that previously reported localized effects could be due to task simplicity and short delay periods and might not generalize. The authors' VGAT-ChR2 bilateral-inactivation strategy probed whether a wide number of bilateral cortical points were necessary for task performance (total 29, ~2 mm radius, Figure 1, size of spots indicates sensitivity to inactivation). They chose three different tasks in a VR T-maze, which was divided into two regions: 2 m cue region (~4 s) where towers can appear on left/right side and a 1 m delay region (~2 s) where no cues are shown. First, in the accumulating-evidence task,

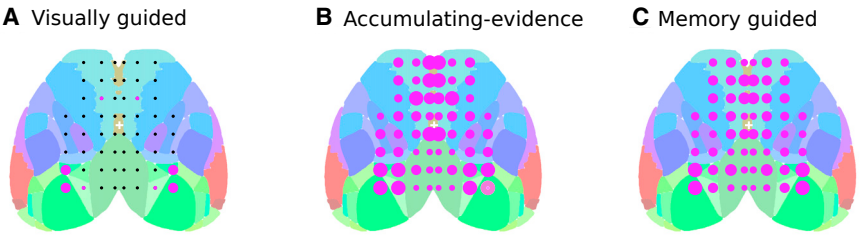

Figure 1. Accumulating-Evidence and Memory-Guided Tasks Are Impaired by Widespread, Whole-Trial Bilateral Inactivation of Cortex (Purple Circle Indicates Impairment Magnitude)
(A) Effect of whole-trial VGAT-ChR2 inactivation at each bilateral-cortical location during the visually guided task were restricted to V1. Circle size represents the magnitude of the performance degradation during local inactivation. Accumulating-evidence task results (B) and memory-guided task (C) indicate that inactivation of widespread areas degrades performance. Bregma is marked with white cross.

a variable number of towers are shown at random locations on their left/right in the cue region as they progress toward the T-junction. Mice must remember the tally of towers during the delay region to choose the side that had more towers for reward. This task demands sensory and memory components. Second, a visually guided task was similar except for a constant stimulus appearing at the end of the tunnel on the side with the reward. Third, a memory-guided task for control wherein the reward-bearing side was indicated (by a tower) in cue region and must be remembered as it disappears in delay region.

The overall success rate of the three tasks was modulated by the amount of cognitive load at 69.3% ± 0.4% accumulating-evidence (n = 36), 73.2% ± 1.4% memory-guided (n = 8), and 92.7% ± 0.6% visually guided (n = 31) tasks. For the accumulating-evidence task, performance was sensitive to even single tower difference on either side. Interestingly, bilateral inactivation of each of the 29 cortical sites significantly degraded performance in the accumulating evidence task. The visually guided task was easiest since there was no accumulation or delay period, and, accordingly, the performance was higher and insensitive to the number of towers appearing in the cue region. Inactivation effects were only found in visual cortex and, to a lesser extent, in medial premotor cortex. To examine the effect of delay, the memory-guided task was added as a control. Interestingly, the performance was closer to the accumulating-evidence task than the visually guided task, suggesting that working memory load during the delay induced significant cognitive demand similar to accumulating evidence. Surprisingly, subsequent inactivation at any of the bilateral cortical points during the memory-guided task resulted in significant performance drops as in the accumulating-evidence task, albeit to a lesser extent (Figure 1). This indicates that post-stimulus memory needs wider areal cortical requirements as compared to the visually guided task. Further, analysis revealed clusters of cortical locations impacting behavioral markers (speed, excess movement, side bias, and performance) that differed among the tasks indicating widely distributed computations specific to task cognitive demand, wherein aspects of behavior were attributed to more distinct cortical regions.

Observing task-related temporal profiles of cortical intracellular Ca^{2+} activity in anatomically defined areas of Emx1-Ai93 mice expressing GCaMP6f revealed distinct dynamics that, in accordance with other studies (Allen et al., 2017), ramped up during the delay region preceding the reward. Increasing task complexity tended to decrease inter-cortical correlated activity, suggesting more independent cortex-wide computations during complex tasks. Hierarchical clustering of the correlations confirmed the formation of independent modules in the accumulating-evidence task compared to the visually guided task. The authors focused on the accumulating-evidence and visually guided tasks for this analysis; a similar analysis of the memory-guided task would have strengthened their argument.

To further assess the requirement of multiple cortical areas in task dynamics, Pinto et al. (2019) turned toward analytical and simulation approaches. These approaches generally confirmed the experimental results and supported the requirement of widespread cortical areas in the accumulating-evidence task. V1 and mV2 contained the most contralateral evidence but were by no means exclusive as decoding weights were widely distributed. Lastly, the authors built a recurrent neural network (RNN) simulation to establish whether computations alone and not the connectivity in a single network of recurrent weights can perform both tasks and whether task load would also affect its ongoing correlational structure as observed *in vivo*. Indeed, the RNN model mirrored *in vivo* results, with the RNN being more sensitive to the inactivation of units in the more demanding task.

Overall, this rigorous and comprehensive work by Pinto et al. (2019) add to a body of evidence indicating that widely distributed cortical computation may be more the norm than the exception. Features of this can be observed in reduced network models, which can adapt to changing demands by re-apportioning existing connectivity. The dependence of some previous task-based work on select cortical areas is intriguing despite the use of delay periods in some studies (Guo et al., 2014; Li et al., 2016; Chen et al., 2017; Gilad et. al. 2018). It is possible that the VR, locomotory nature, and the use of bilateral inactivation of the Pinto et al. (2019) task are potential explanations for the observed widespread distribution of causally associated cortical areas in the accumulating-evidence and memory-guided tasks.

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