DECISION-MAKING

A visuomotor microcircuit in frontal cortex

Visually guided behavior begins with inputs to sensory cortices, but the decision to initiate actions engages the frontal cortex. A new study dissects a microcircuit for visual-to-motor transformation in the anterior cingulate cortex of the mouse with implications for impulsivity and disease states.

Heather K. Ortega and Alex C. Kwan

Many decisions are made by taking in sensory information and transforming it into motor output. An animal will hear a predator approaching and hide. A pedestrian will see a car coming and wait to cross the street. These decisions likely rely on computations in the sensory and frontal cortices, as well as their interactions. In the mouse, there are extensive reciprocal connections between posterior sensory areas and medial frontal regions, including the anterior cingulate cortex (ACC) and secondary motor cortex (M2), with parallel pathways for the different perceptual modalities including vision[1,2] and audition[3]. Thus far, early works have mostly studied the circuitry from the perspective of feedback provided by top-down modulation. However, recent evidence suggests that the bottom-up transmission of information may also be crucial for behavior. For instance, cortex-wide imaging revealed visually and auditory evoked activity in mouse ACC and M2 during perceptual tasks[4,5]. A new study in this issue of *Nature Neuroscience* tackles the circuit from the bottom-up direction, methodically uncovering the stages of neural processing through which visual inputs are converted to goal-directed actions in the medial frontal cortex[6].

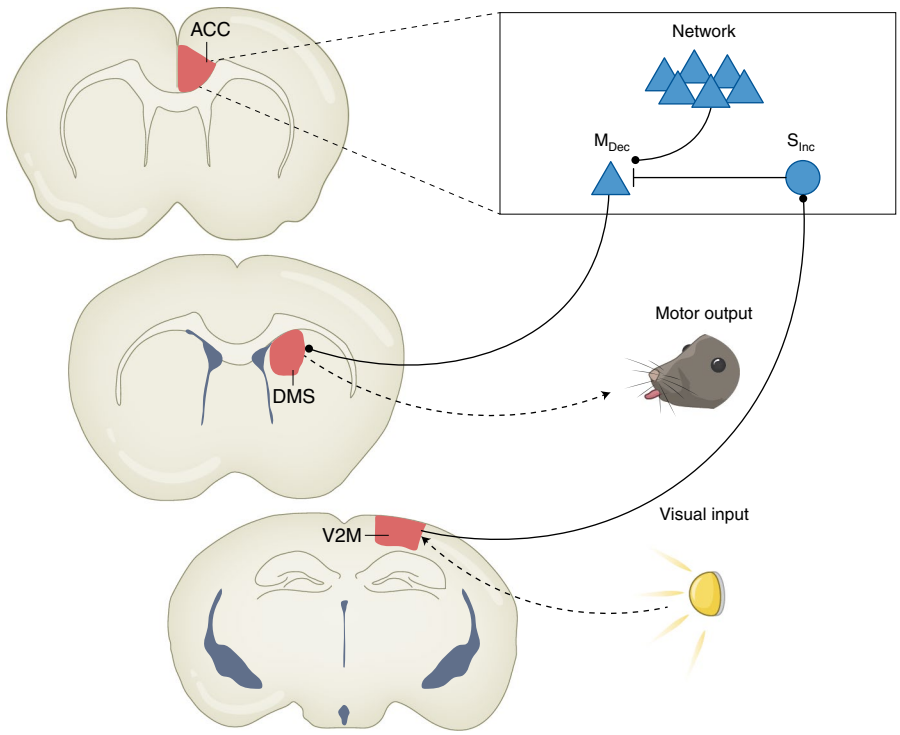

Fig. 1 | A visuomotor microcircuit. During task-related perceptual licking, visual input is transmitted from the medial secondary visual cortex (V2M) to the anterior cingulate cortex (ACC). In the ACC, when excitatory network activity is low, S_{Inc} sensory neurons inhibit M_{Dec} motor neurons in a sensory-to-motor transformation step. Finally, the premotor signal is transmitted from M_{Dec} neurons to the dorsomedial striatum (DMS) and eventually produces voluntary movement.

To dissect the neural underpinnings of perceptual decision-making, Kim and colleagues trained animals to perform a visual go/no-go task, in which fluid-restricted mice should lick only after observing a flashing light stimulus to receive a water reward. Impulsivity was characterized by premature licking during go trials, and false alarm by licking during no-go trials. Given the wide range of possible regions involved in this visually guided behavior, authors took a broad approach and silenced a variety of cortical areas to assess task involvement. The $GABA_A$ receptor agonist muscimol was used to pharmacologically silence excitatory activity to test the role of five different cortical brain regions. The authors found that inactivating the ACC or visual cortical regions impaired the mouse's performance but, interestingly, through different deficits: ACC inactivation exacerbated the number of impulsive responses, whereas silencing visual cortical regions reduced responses across all trial types, consistent with loss of visual perception. This was the first hint that ongoing activity in the ACC is important for mitigating impulsivity.

With their focus narrowed to the ACC, Kim and colleagues moved on to measuring task-related neural dynamics in ACC. Silicon electrodes were used to record spiking activities in behaving mice. The authors classified cells into sensory- (S) and motor-related (M) neurons based on their firing rate changes in response to visual stimuli and licking, respectively. Exploiting the inherent trial-to-trial variability in response times, they discovered that the S and M neurons have unique spiking dynamics around the time of a visually evoked lick response. Among the M neurons, a subset had decreased activity (M_{Dec}) preceding the sensory-cue-evoked lick during the task, with the time to spike rate threshold reliably predicting the lick timing. For the S neurons, a subpopulation (S_{Inc}) showed a correlation of increasing firing rates with earlier response times. The close relationship between the spiking dynamics

seen in M_{Dec} and S_{Inc} neurons and the response times indicated that these ACC cell types are the building blocks for the sensory-to-motor transformation.

The firing patterns of M_{Dec} and S_{Inc} neurons suggested a microcircuit organization in the mouse ACC in which S_{Inc} neurons would receive sensory inputs and in turn suppress the firing of M_{Dec} neurons. After reaching a threshold, suppression of M_{Dec} neurons would release the motor output. Several additional pieces of evidence supported and further elaborated this scheme. The majority of the S_{Inc} neurons had narrow spike waveforms, marking them as putative fast-spiking GABAergic interneurons. Interestingly, during miss trials, S_{Inc} neurons increased firing, but this was not followed by suppression of M_{Dec} neurons and licking. How can a microcircuit result in suppression of M_{Dec} neurons in some cases but not others? Questions such as these led Kim and colleagues to search for a possible gating mechanism. During spontaneous licks, there was still a significant, but small, increase in S_{Inc} activity accompanying the suppression of M_{Dec} neurons. In this situation, the authors found a concomitant reduction of overall network activity in ACC that correlated with response times, and may therefore be a parallel input to M_{Dec} neurons (in addition to the contribution from S_{Inc} neurons) to spur the spontaneous lick in the absence of a visual stimulus. Here, excitatory network activity gates the sensory-to-motor transformation made by S_{Inc} and M_{Dec} neurons (Fig. 1).

Now that the microcircuit is defined, where does the sensory input come from? And where do the motor signals go? Anatomical tracing using retrogradely transported viruses indicated that a main source of inputs for the mouse ACC is the medial secondary visual cortex (V2M). Using optotagging, Kim and colleagues confirmed that many of the ACC neurons postsynaptic to V2M inputs were S_{Inc} cells and had fast-spiking waveforms. Consistent with the hypothesized microcircuit, optogenetic stimulation of the V2M axonal terminals in the ACC induced licking when the mouse was engaged in the task. For the output, the authors focused on projection from ACC to the dorsomedial striatum (DMS). Multichannel recordings in DMS revealed subsets of neurons that showed a significant motor-related activity before licking. Notably, photostimulation of the V2M axons in ACC could elicit firing in DMS. The exact mechanism that drives movement is unclear, although it could involve fast-spiking cells in the striatum, as optogenetic activation of ACC-to-DMS neurons led to increased firing of the fast-spiking cells in DMS. Together, these experiments demonstrate the likely long-range input sources and output targets for the ACC visual-to-motor microcircuit (Fig. 1).

Looking forward, the study by Kim and colleagues points to at least several gaps in current knowledge that could inspire future research directions. The medial frontal cortex, including the ACC and M2, not only send efferents to the dorsomedial striatum, but also project to other motor-related regions in the basal ganglia and superior colliculus, as well as the brainstem via pyramidal tract[7]. One key question is how the frontal-striatal projection highlighted in the current study may coordinate with other efferent pathways to bias motor outputs. In particular, the frontal-collicular pathway relays choice-related information and appears to be important for action selection during motor planning and execution[8,9]. Moreover, in a similar go/no-go paradigm, frontal cortical neurons projecting to the subthalamic nucleus of the basal ganglia were preferentially active during no-go trials, and optogenetic activation reduced impulsive licking[10]. Thus, there are multiple output pathways originating from the medial frontal cortex that can bias action, including specifically the inhibition of impulsive action. It is possible that there are microcircuit mechanisms within the medial frontal cortex to arbitrate between these different outputs, such that the appropriate motor response is produced to meet behavioral demands.

Classically there is a dichotomy of motor actions: externally cued versus self-initiated. Externally cued actions are responses conditional on a task-relevant sensory stimulus. In contrast, self-initiated actions are intentional movements with the response timing determined by the animal. An earlier study, based on a clever task with self-paced action, showed that neurons in the M2 region of the medial frontal cortex exhibit two main types of spiking responses: one population has ramp-to-threshold activity akin to an integrator, and a second population shows transient activation that may serve as input to the integrator[11]. Intriguingly, these integrator and transient response subtypes resemble the M_{Dec} and S_{Inc} neurons described by Kim et al. in the current study[6]. Do externally cued and self-initiated action rely on the same microcircuit mechanisms to produce motor output? May the same subpopulations of neurons perform the integrator and transient functions in both situations? Future studies may answer these questions using context-dependent tasks in which animals are required to toggle between sensory-cue-guided and non-contingent responses[12]. Moreover, the sensory-cue-to-motor association is learned, and therefore prior experience must play an essential role in shaping and strengthening the appropriate microcircuitry in the medial frontal cortex[13].

To summarize, the new work by Kim et al.[6] defines a microcircuit in the mouse ACC that is important for transforming visual inputs into goal-directed actions. Normal activity in the ACC is key for inhibiting impulsive responses, and transient dips in the activity of motor-related neurons gate the initiation of goal-directed actions. Maladaptive alterations in this gating mechanism may underlie a range of neuropsychiatric states. For example, drug-seeking behavior is often associated with impulsivity. Numerous studies have linked long-term exposure to drugs of abuse to frontal-striatal circuit dysfunction and the loss of inhibitory response control[14]. Furthermore, chronic stress promotes repetitive responding at the expense of goal-directed actions. This form of motivational anhedonia is a core symptom of depression and occurs in lock step with progressive stress-induced alterations of activity dynamics in the medial frontal cortex[15]. Therefore, not only is the visuomotor microcircuit essential for performance in perceptual tasks, but its disruption may also underpin aspects of mental illnesses. ❐

Heather K. Ortega[1] and Alex C. Kwan[2,3] ✉

[1]Interdepartmental Neuroscience Program, Yale University School of Medicine, New Haven, CT, USA. [2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA. [3]Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA.

✉*e-mail: alex.kwan@yale.edu*

Published online: 19 August 2021

https://doi.org/10.1038/s41593-021-00915-4

References

1. Zhang, S. et al. *Science* **345**, 660–665 (2014).
2. Leinweber, M., Ward, D. R., Sobczak, J. M., Attinger, A. & Keller, G. B. *Neuron* **95**, 1420–1432 e1425 (2017).
3. Schneider, D. M., Nelson, A. & Mooney, R. *Nature* **513**, 189–194 (2014).
4. Musall, S., Kaufman, M. T., Juavinett, A. L., Gluf, S. & Churchland, A. K. *Nat. Neurosci.* **22**, 1677–1686 (2019).
5. Mohajerani, M. H. et al. *Nat. Neurosci.* **16**, 1426–1435 (2013).
6. Kim, J. H., Ma, D. H., Jung, E., Choi, I. & Lee, S. H. *Nat. Neurosci.* https://doi.org/10.1038/s41593-021-00910-9 (2021).

7. Barthas, F. & Kwan, A. C. *Trends Neurosci.* **40**, 181–193 (2017).
8. Duan, C. A. et al. *Nat. Commun.* **12**, 2727 (2021).
9. Huda, R. et al. *Nat. Commun.* **11**, 6007 (2020).
10. Li, B., Nguyen, T. P., Ma, C. & Dan, Y. *Proc. Natl. Acad. Sci. USA* **117**, 17278–17287 (2020).
11. Murakami, M., Vicente, M. I., Costa, G. M. & Mainen, Z. F. *Nat. Neurosci.* **17**, 1574–1582 (2014).
12. Siniscalchi, M. J., Phoumthipphavong, V., Ali, F., Lozano, M. & Kwan, A. C. *Nat. Neurosci.* **19**, 1234–1242 (2016).
13. Makino, H. et al. *Neuron* **94**, 880–890 e888 (2017).
14. Jentsch, J. D. & Taylor, J. R. *Psychopharmacology (Berl.)* **146**, 373–390 (1999).
15. Barthas, F. et al. *Biol. Psychiatry* **88**, 541–553 (2020).

Acknowledgements

This work was supported by US National Institute of Mental Health grants R01 MH112750 and R21 MH118596 (A.C.K.), a Simons Foundation Autism Research Initiative Pilot Award (A.C.K.), a Gruber Science Fellowship (H.K.O.) and US National Institutes of Health training grant T32NS007224 (H.K.O.).

Competing interests

The authors declare no competing interests.