Stentiford, R., & Cerminara, N. L. (2019). Timing Rewarding Movements. *Neuron*, *103*(3), 358-360. https://doi.org/10.1016/j.neuron.2019.07.024

Timing rewarding movements

Rachael Stentiford and Nadia L Cerminara*

School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK

*Corresponding author: n.cerminara@bristol.ac.uk

Summary

Preparatory activity is found across the motor network. In this issue of Neuron, Chabrol et al., (2019) show that preparatory activity in the anterior lateral motor cortex (ALM) and cerebellum is related to the prediction of reward delivery and that the cerebellum provides a learned timing signal to the ALM.

Main text

In day to day life we are constantly conducting goal directed movements, whether that be throwing a ball, reaching for a cup of coffee or even typing on a keyboard, perfecting those movements is inherently rewarding. The cerebellum is thought to have a hand in this process, learning to time our actions by generating internal models – neural representations – of the body and its interaction with the world, predicting the sensory outcomes of an action and comparing them with sensory input to refine future movements . The cerebellum can store multiple internal models and can select a model depending on the behavioral context required.

Motor planning leading up to goal directed movements has been found across the motor network. One such area in rodents is the anterior lateral motor neocortex (ALM), which may have functional similarities to the primate premotor cortex and is an area shown to be important for planning of voluntary movements (Guo *et al.*, 2017). ALM neurons exhibit preparatory activity before movement and maintenance of this activity is dependent on a bidirectional connection with the motor thalamus (Guo *et al.*, 2017, Fig. 1). The significance of this preparatory activity is not well understood but it is thought to link past events with future movements (Guo *et al.*, 2017). For example, when faced with the decision of 'should I throw the ball to my friend using an over- or under-arm technique' during a game of catch, our brains use a combination of sensory input (is my arm fatigued by our game of catch, how far away is my friend) and recent reward history (the last time I threw the ball to my friend they dropped a high throw) to help decide which action to take. The ALM may represent a key node in the motor network that is crucial in selecting motor actions.

ALM projects to the cerebellum via the basal pontine nuclei and the output of the cerebellum via the cerebellar nuclei project to the motor thalamus (Fig. 1), thereby allowing the two brain regions to form closed-circuit loops (Gao *et al.*, 2018). How the ALM and cerebellum work cooperatively to ensure the success the of a goal orientated movement is unknown and is explored in this issue of Neuron by Charbrol et al., (2019).

Combining behavior, optogenetics and neural recordings, Chabrol et al., (2019) recorded from the ALM and cerebellum of mice running in a virtual reality corridor. The mice learnt to associate a visual cue with a reward delivered 40 cm further along the virtual track. Preparatory activity was observed prior to reward delivery that precedes movement in a subset of ALM neurons and in the dentate nucleus (DN), as previously described by (Guo *et al.*, 2017; Gao *et al.*, 2018).

Chabrol et al. (2019) then examined the influence of dentate nucleus (DN) activity on ALM preparatory firing by manipulating inhibitory Purkinje cell (PC) input to the DN optogenetically alongside DN and ALM recordings (Fig. 1). Photoactivating PCs in a region known to both receive visuomotor inputs and that projects to the DN for 1 second preceding the reward point inhibited DN activity and subsequently interrupted ALM preparatory activity.

While the observation that activity in the DN precedes movement has been shown previously (e.g. Thach, 1975), the finding that this preparatory increase in both DN and ALM may be related to the timing of reward is novel, as the preparatory activity was only observed in the rewarded section of the virtual corridor, emerged prior to reward delivery and was not related to running speed or licking events outside of the reward zone. Because the timing of the reward is dependent on how slowly or quickly the mice reach the reward following the visual cue for reward, the authors predicted that if preparatory activity is related to the timing of reward, then activity for slow trials should start earlier and conversely, faster trials should start later. This is precisely what Charbrol et al., (2019) were able to demonstrate.

The study by Charbrol et al., (2019) adds to a growing literature demonstrating that neural correlates related to reward are signaled within the cerebellum (Wagner *et al.*, 2017; Heffley *et al.*, 2018; Kostadinov *et al.*, 2019). PCs receive inputs via two major pathways: climbing fiber (CF) inputs from the inferior olive (IO) and mossy fiber (MF) inputs via granule cells (GrC) which are thought to carry sensory and motor information from the neocortex and periphery (Fig. 1). Reward anticipatory activity has been recorded in GrCs (Wagner *et al.*, 2017). CFs are thought to provide a teaching signal to PCs which is used to update internal models in motor learning. CFs trigger complex spikes in PCs; Chabrol et al., (2019) examined the CF to PC response by using the presence of so called ‘fat spikes’ in their cerebellar recordings as a proxy for CF activity and found an increase in the frequency of fat spikes at reward delivery. This is consistent with recent work by Heffley et al., (2018) and Kostadinov et al., (2019), who both observed CF activity associated with reward expectation and delivery arranged in a topographical manner within the forelimb controlling areas of the cerebellum. Charbrol et al., (2019) suggest that the cortico-ponto-cerebellar pathway relays relevant visual and motor activity from the neocortex to combine with reward prediction signals from the GrCs. Learning in the cerebellum is often attributed to plasticity at parallel fiber (PF) to PC synapses under the control of CF signals. Thus, the CFs which provide reward timing signals may refine the timing of preparatory activity at the PF to PC synapse. Charbrol et al., (2019) concluded that after having learned to predict upcoming rewards, cerebellar output via the DN contributes to the precise timing of preparatory signals in the ALM to refine goal directed movement. An alternative hypothesis that could be considered is that the cerebellum provides a signal related to the success or failure of the chosen internal model via the DN output. This is then related to the ALM via the motor thalamus to shape decisions on future goal directed movements.

Outstanding questions following on from this study and those that recently have shown that the cerebellum is involved in the signaling of reward. 1) Are dopamine neurons involved in the association between reward and a goal directed movement? Although dopaminergic projections to the basal ganglia and dopamine dependent reinforcement learning based on reward prediction errors are well known (Schultz *et al.*, 2017), dopaminergic projections have been shown to project to the cerebellar cortex (Ikai *et al.*, 1992) and the cerebellar nuclei are known to project to midbrain dopaminergic neurons (Carta *et al.*, 2019). Viral and optogenetic strategies targeting dopaminergic inputs to the cerebellum during reward based task would shed light on this question. 2) How does preparatory activity in the ALM and DN develop as the mice learn to associate the cue and reward? Recordings from both brain regions throughout learning may help to shed light on how preparatory activity is acquired and over what time scale. 3) Is preparatory activity related to reward found in other areas of the cerebellum or is it unique to the parts of the cerebellum now thought to be involved in higher cognitive functions ? 4) If the signal from the DN reflects a timing signal, how will this affect behavior? Addressing this would be pertinent as a lack of behavioral effect was evident when inactivating the DN with photoactivation of the overlying PCs in the tasks used by Charbrol et al., (2019) and by Gao et al (2018) who found no behavioral deficits in a sensory discrimination task. Regardless of the outstanding questions, the findings are an important step toward understanding how motor networks interact to contribute to the preparatory activity related to precise timing of goal directed behaviors and reward.

References

Carta, I., Chen, C.H., Schott, A.L., Dorizan, S. & Khodakhah, K. (2019) Cerebellar modulation of the reward circuitry and social behavior. Science, *363,*6424

Chabrol, F.P., Blot, A. & Mrsic-Flogel, T.D. (2019) Cerebellar Contribution to Preparatory Activity in Motor Neocortex. Neuron.

Gao, Z., Davis, C., Thomas, A.M., Economo, M.N., Abrego, A.M., Svoboda, K., De Zeeuw, C.I. & Li, N. (2018) A cortico-cerebellar loop for motor planning. Nature *563*, 113-116.

Guo, Z.V., Inagaki, H.K., Daie, K., Druckmann, S., Gerfen, C.R. & Svoboda, K. (2017) Maintenance of persistent activity in a frontal thalamocortical loop. Nature *545*, 181-186.

Heffley, W., Song, E.Y., Xu, Z., Taylor, B.N., Hughes, M.A., McKinney, A., Joshua, M. & Hull, C. (2018) Coordinated cerebellar climbing fiber activity signals learned sensorimotor predictions. *Nat Neurosci. 21*, 1431-1441.

Ikai, Y., Takada, M., Shinonaga, Y. & Mizuno, N. (1992) Dopaminergic and non-dopaminergic neurons in the ventral tegmental area of the rat project, respectively, to the cerebellar cortex and deep cerebellar nuclei. Neuroscience *51*, 719-728.

Kostadinov, D., Beau, M., Pozo, M.B. & Hausser, M. (2019) Predictive and reactive reward signals conveyed by climbing fiber inputs to cerebellar Purkinje cells. Nat Neurosci. *22*, 950-962.

Schultz, W., Stauffer, W.R. & Lak, A. (2017) The phasic dopamine signal maturing: from reward via behavioural activation to formal economic utility. Curr Opin Neurobiol. *43*, 139-148.

Ohach, W.T. (1975) Timing of activity in cerebellar dentate nucleus and cerebral motor cortex during prompt volitional movement. Brain Res. *88*, 233-241.

Wagner, M.J., Kim, T.H., Savall, J., Schnitzer, M.J. & Luo, L. (2017) Cerebellar granule cells encode the expectation of reward. Nature, *544*, 96-100.

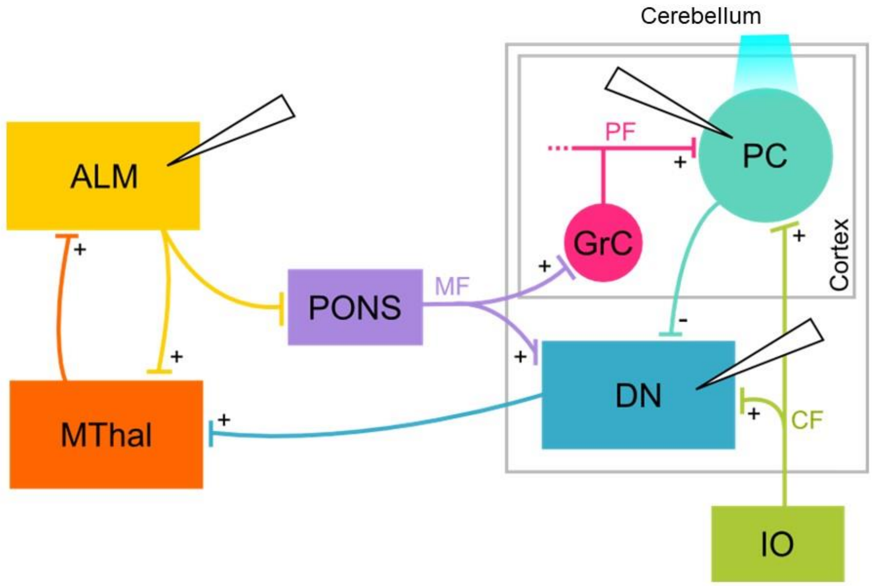

Figure 1: Summary of circuit involved in the generation and maintenance of preparatory activity related to reward in the ALM and cerebellum. motor thalamus (MThal); cerebellar granule cells (GrC); parallel fiber (PF), climbing fiber (CF), inferior olive (IO), Purkinje cells (PC), dentate nucleus (DN); See main text for further details.