NEUROSCIENCE

COMMENTARY

M. Salgado-Ménez, V. de Lafuente / Neuroscience 482 (2022) 159–160

Purkinje Cells are Key for Rhythmic Predictions in the Cerebellum

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Keywords: Cerebellum, Timing, Predictive activity.

In a study published in this issue of Neuroscience, the authors demonstrate a marked reduction in sensory-predictive activity within cerebellum that arises from a GABA antagonist infusion that diminishes the influence of Purkinje cells over dentate nucleus (DN) neurons (see Fig. 1).

Music, speech, and effective motor actions rely to a great extent on the brain's ability to perceive regularities and predict future sensory events. Predictive activity within the brain allows the timely coordination of our movements with the ever-changing world round us. The precise timing and fine adjustment of motor commands that are required to adequately interact with the environment are carried in the cerebellum, a brain structure in which sensory feedback and motor actions are compared to generate error-based adjustments and learning. This crucial role is demonstrated in cerebellar patients, who show a decreased capacity to perform the precise repetitive movements needed to tap in sync with a metronome (Franz et al., 1996). We learned recently that neurons in the dentate nucleus (DN), one the major output nuclei of the cerebellum, exhibit periodic modulations of activity that are predictive of the onset time of a regularly repeating visual stimulus (Ohmae et al., 2013; Uematsu et al., 2017). It has been hypothesized that this oscillatory activity results from the dynamic balance of inhibitory signals, coming from Purkinje cells in the cerebellar cortex, and the excitatory inputs generated in the brainstem and carried into the cerebellum by the climbing and mossy fibers (Schonewille et al., 2021). But how does the cerebellum balance these signals arising from two different sources? Which one is responsible for generating the prediction of upcoming sensory stimuli?

To gain insight into these questions, Uematsu and Tanaka (2022) recorded from DN neurons in monkeys trained to perform an omission detection task (also called a missing oddball paradigm). In this task, monkeys had to perform a saccadic eye movement in response to the omission of a sensory stimuli that was being flashed at regular intervals in the screen (Tanaka, 2006). The authors fist corroborated that the presence of a rhythmic sensory stimulus induced regular oscillations in neuronal activity (Ohmae et al., 2013; Tanaka et al., 2021), and that the peaks of this activity predicted the time of the next stimulus (Kameda et al., 2019). Then, by using a custom-built injectrode they infused small amounts of either GABA or glutamate antagonists in vicinity of the neurons being recorded in the DN (gabazine or NBQX-CPP, respectively). The authors observed that, by blocking the strong GABAergic input that arises from Purkinje neurons located the cerebellar cortex, the periodic activity of DN neurons significantly decreased in amplitude. This observation is consistent with the idea that Purkinje cells have a key role in generating predictive activity furnished by the cerebellum. Importantly, the predictive activity of DN neurons is broadcasted through the thalamus to reach neocortical areas like the motor, premotor, and prefrontal cortices. In sharp contrast to the effects of gabazine, the authors found that decreasing the influence of excitatory inputs (infusion of NBQX-CPP) had no consistent effect on the oscillatory activity of DN neurons. This important observation indicates that the excitatory inputs coming from the collaterals of the climbing and mossy fibers are not essential for the generation of the oscillatory predictive activity of DN neurons.

These results pose important constrains on computational models aimed to mechanistically explain information processing in the cerebellum, and are consistent with the view that timed disinhibition of DN neurons might be responsible for their transient activation observed during movement (Ishikawa et al., 2014). It is important to note that the effects of gabazine on DN neuron activity could partly be mediated by interneurons (Uusisaari et al., 2007; Uusisaari and De Schutter, 2011). Thus, future research involving cell-type specific manipulation is necessary, which should also address the lack of concomitant behavioral changes resulting from the pharmacological manipulations of DN neurons, an observation probably explained by the small volumes of the injected antagonists. The importance of oscillatory sensory-predictive signals, observed by the

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https://doi.org/10.1016/j.neuroscience.2021.12.007

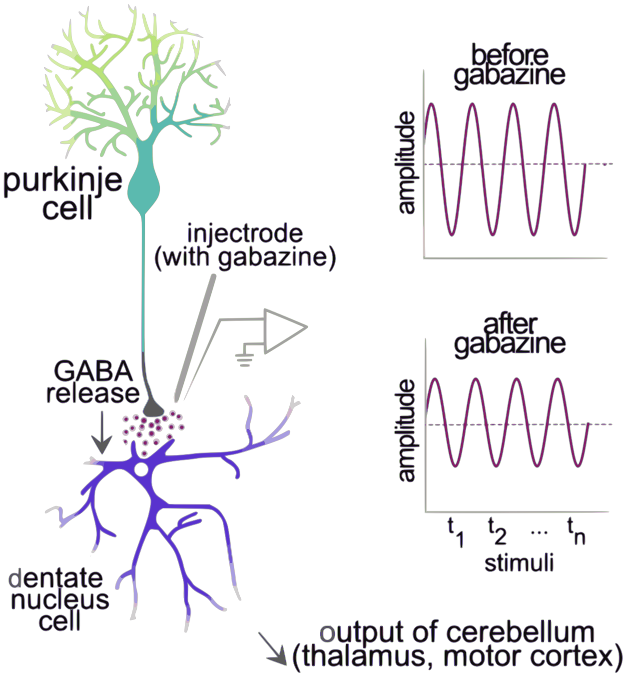

Fig. 1. The authors injected a GABA antagonist (gabazine) in the vicinity of dentate nucleus neurons. This antagonist markedly reduced the influence of Purkinje neurons over the dentate nucleus, which resulted in a reduction of the oscillatory activity that is related to the prediction of regularly timed sensory stimuli. This illustrates the importance of Purkinje neuron in the predictive capacity of the cerebellum.

authors in the cerebellum, is highlighted by the fact that these types of signals are observed in numerous neocortical and subcortical structures in the context of behavioral tasks that require rhythm entrainment with external or internal metronomes (Bartolo et al., 2014; Cadena-Valencia et al., 2018). The authors' observations indicate that DN neurons in the cerebellum might be a key processing node for the generation of rhythm and the perception of regularities in sensory stimuli.

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