How the brain plays musical statues

Yaara Lefler[1] and Tiago Branco[1,*]

[1] UCL Sainsbury Wellcome Centre for Neural Circuits and Behaviour, London, W1T 4JG, UK

* For correspondence: t.branco@ucl.ac.uk

A study by Goñi-Erro et al. has found that activating a specific subpopulation of glutamatergic neurons in the brainstem issues a motor command for global motor arrest. This motor arrest is distinct from defensive freezing and has a striking pause-and-play pattern accompanied by a reduction in respiration and heart rate.

In the children's game musical statues, players dancing to music must abruptly interrupt their dance moves and stay still for as long as the music is paused. If the person in charge of the music spots anyone moving after the music stopped, that player is eliminated. When the music plays again, the remaining participants resume their dance from the point where they paused it. The winner is the last player standing, presumably the person who has mastered the skills of interrupting ongoing movement with the fastest reaction time and holding the pose perfectly still for as long as it is required.

While the survival value of mastering musical statues may be limited to toddlers competing for sweets at birthday parties, the rapid arrest of ongoing movement is an important feature of natural behaviour for most animals. For example, foraging behaviour is not one long continuous movement but a set of actions punctuated by pauses. These pauses may happen in response to a salient sensory cue in the environment, so that the cue is attended to and potentially triggers a re-evaluation of the current goal-action plan. Pauses in locomotion can also be a defensive response to a threatening stimulus or they may happen because the current goal of the motor program has been reached. The ability to stop motion is critical for stopping undesired and executing suitable actions, a neural function that is disrupted in pathologies characterized by impaired motor control such as Parkinson’s Disease or Tourette’s Syndrome.

A new study by Goñi-Erro and colleagues[1] has discovered a small group of neurons in the mouse brainstem that, when activated, triggers an instantaneous pause of motor behaviour. Sustained activation of these neurons causes the animal to stay still and maintain the body posture it had at the time of motion interruption, and the release of activation leads to a seemingly smooth continuation of the movement from the position it was interrupted in.

Quickly stopping ongoing motor behaviour and standing still is not trivial. Indeed, maintaining a still posture requires continued feedback and precise control of muscle activity, just as precise as during movement execution[2]. This phenomenon is called global motor arrest.

Previous work has characterized the role of neural circuits such as the ventrolateral periaqueductal gray (vlPAG) in eliciting the arrest occuring during defensive freezing[3]. The neural processes that control motor arrest in other natural behaviours, however, have remained elusive. For ambulatory animals, locomotion is arguably the most important behaviour to be initiated and stopped, and In mammals, the brainstem mesencephalic locomotor region (MLR) is the key centre for controlling spinal cord circuits that generate locomotor patterns. Within the MLR, the pedunculopontine nucleus (PPN) has been previously identified as a neural circuit that can inhibit movement. Activity manipulations of the PPN, however, have led to conflicting views, with many studies reporting that it can cause locomotion initiation or modulation of ongoing locomotor patterns, differences that hint at a heterogeneous function of the PPN[4,5].

In this new study, Goñi-Erro and colleagues[1] have found that the PPN contains neurons specialized in the control of global motor arrest. They focused on a subset of glutamatergic cells expressing the transcription factor Chx10 and previously shown to be involved in motor-related tasks[6-9].

In the first set of experiments, the authors crossed a Chx10-Cre mouse line with a mouse reporter line to visualize $Chx10^{+}$ neurons and found them primarily in the

rostral PPN. They then expressed the excitatory opsin ChR2 in Chx10-PPN neurons and optogenetically activate this population to test the effects on the mouse locomotor behaviour in a linear corridor, as well as in a cylindrical arena to evaluate other behaviours such as grooming and rearing. The activation of Chx10-PPN neurons caused an arrest of all ongoing motor behaviours and this effect exceptionally robust - it occurred on every trial in every tested mouse.

To assess whether the Chx10-PPN - induced motor arrest occurs in any point of the step cycle or in specific postures, the authors performed kinematic analyses using video recordings from side and bottom views to capture the position of limbs and paws and combined it with EMG recordings of flexor and extensor muscles. The rigor and depth of this multidimensional quantitative analysis is a standout feature of this study and showed that Chx10-PPN activation can stop locomotion at any point of the step cycle and, surprisingly, the coordination pattern between flexor and extensor muscles is sustained throughout the arrest. In other words, Chx10-PPN neurons effectively pause locomotor activity, which suggests that Chx10- PPN neurons issue a general motor command for global arrest.

If the locomotion is paused by Chx10-PPN activation, what happens when the break is released? Remarkably, analysis of the pattern after termination of the optogenetic stimulation showed that stepping resumes from where it had paused, showing that the mouse nervous system keeps a memory of the action and can then resume its completion smoothly. The authors call this phenomenon a pause-and-play pattern, which also holds for other motor behaviours, such as grooming.

Since the PPN has a role in autonomic regulation, Goñi-Erro et al. then used whole-body plethysmography and wireless electrocardiography (ECG) to monitor breathing and heart rate, respectively. They found that during motor arrests there was a drastic decrease in respiration, causing apnoea, and bradycardia. To determine whether these effects were directly related to the stimulation or a secondary consequence of motor arrest, the authors performed the same experiments in anesthetised mice. These experiments showed that while the effects on heart rate were milder under anaesthesia, the respiratory effects remained strong, suggesting that motor arrest and apnoea are directly coupled at neural level.

The striking paus-and-play arrest pattern generated by Chx10-PPN activation contrasts with freezing in face of a threat, when mice usually display a characteristic crouching, alert posture. The vlPAG – a major centre for initiating defensive freezing – is known to also have glutamatergic neurons that express Chx10[6,7]. Activating Chx10-vlPAG neurons resulted in motor arrest, but in a pattern that resembles defensive freezing. The mice stopped in the same stereotyped position, with both hindlimbs in stance. Upon termination of stimulation, mice stayed immobile for long periods of time and then eventually restarted locomotion with a new step cycle. In conclusion, different types of global motor arrest have specific neural pathways, with Chx10-vlPAG neurons regulating defensive freezing and Chx10-PPN triggering pause-and-play motor arrests. This kind of labour division has been previously suggested for defensive and exploratory locomotion at the level of the MLR[10-12].

The mechanisms underlying pause of movement is unclear, but Goñi-Erro et al. provide a good starting point. Using anterograde tracing, they observed very sparse direct projections of the Chx10-PPN neurons to the spinal cord and no projections across hemispheres in the brain. Since motor arrest could be triggered by unilateral stimulation of Chx10-PPN neurons, these observations narrow down the list of downstream targets to regions that receive bilateral projections, such as the pontine reticular nuclei, the gigantocellular reticular nuclei, and the raphe magnus. The authors speculate that a possible circuit mechanism for arrest initiation could thus be activation of neurons in some of these circuits[13], and that the excitation of rhythm generating circuits in the spinal cord might involved in the maintenance of the paused point in the step cycle, effectively locking movement in phase until the excitation is removed. The tracing experiments also showed that Chx10-PPN neurons project to areas known to control respiration, such as the pre-Bötzinger complex[14], providing a direct circuit link between global motor arrest and breathing rate.

Most of the results in this study are generated using optogenetic stimulations, which can cause artificial neural activity patterns. Notably, Goñi-Erro et al. observed that mice undergo spontaneous locomotor arrest coupled with apnoeic events and bradycardia, whose frequency was decreased by ablation of Chx10-PPN neurons.

These results suggest that the pause-and-play global motor arrest occurs during natural behaviour. It would be interesting to explore ethologically relevant contexts where spontaneous pause-and-play arrests might be more prominent, perhaps by explicitly delivering unexpected sensory stimuli during foraging while also playing with the motivational value of such stimuli. Neural activity recordings from Chx10-PPN neurons in these conditions could lead to the understanding of their activity profile and the underlying mechanisms leading to the activation of this subset of neurons during natural global motor arrests. Nonetheless, the ability of a single neural population to robustly paus locomotor behaviour at any point of the step cycle is fascinating. It provides a starting point for investigating how a command for motor arrest orchestrates downstream circuits to pause and resume behaviour, and perhaps also a strategy to crush it at musical statues.

Conflict of interests.

The authors declare no conflict of interests.

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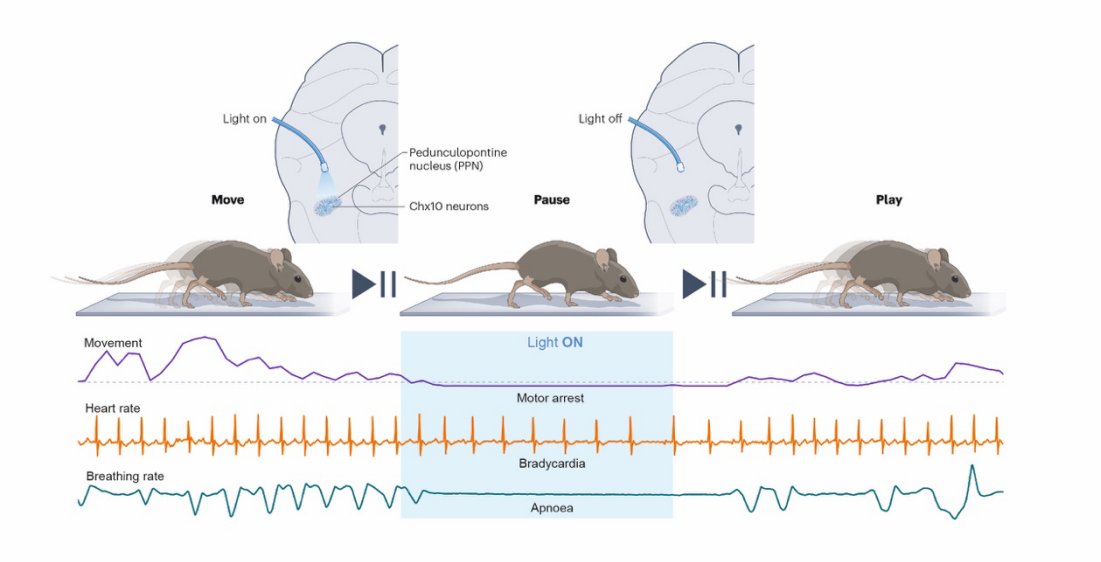

Fig 1. Activation of Chx10 neurons in the pedunculopontine nucleus causes global motor arrest.

Top: optogenetic activation of ChR2-expressing Chx10-PPN cells causes an immediate motor arrest that persists throughout the duration of light stimulation. The arrest is characterised by a “pause-and-play” pattern: mice pause and sustain the posture they had at the time of light onset, and resume the locomotor cycle at light offset.

Bottom: the light-evoked motor arrest is accompanied by autonomic regulation. Top trace: activity tracking from a video recording showing inactivity during light stimulation (shaded blue). Middle and lower traces: whole-body plethysmography shows a reduction in breathing rate (apnoea) and electrocardiography recordings show a decrease in heart rate (bradycardia) during light stimulation. In this example, the duration of light stimulation is 1 sec.