The cost of sensory loss: irreversible motor deficits scale with the degree of proprioceptor ablation

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Summary

Proprioception, the sense of body position and movement, is essential for robust motor control. We used a genetically engineered mouse model to acutely ablate proprioceptive neurons and studied the effects on locomotion using high-resolution kinematics. Within 72 hours of ablation, locomotor performance was severely impaired, with only 16% of animals retaining the ability to reach high speeds (i.e. 0.9 m/s). Gait impairment persisted throughout the 60-day observation period, with no signs of recovery. Histological analysis revealed a direct correlation between the temporal dynamics of cell ablation and motor deficits. Our results highlight the critical role of proprioception in controlling locomotor function and underline its limited compensatory capacity up to two months after acute loss.

Introduction

Sensory cues are essential to navigate robustly through complex environments. Locomotion, on which we rely heavily in our daily lives, depends on the detection and processing of somatosensory information from mechanoreceptors in the skin (i.e. cutaneous) and muscles (i.e. muscle spindles and Golgi tendon organs or GTO) to the central nervous system [1]. Muscle spindles and GTO provide continuous "proprioceptive" feedback about the length, tension, and position of our muscles and joints [2] and play a critical role in ensuring robust locomotor control [3], [4]. Not surprisingly, proprioception is currently central to research areas related to spinal cord injury, prosthetics, robotics and neurodegenerative diseases [5], [6], [7]. But can recovery occur after sudden proprioceptive sensory loss? We used a combination of mouse genetics and high-resolution biomechanics to study the effects of muscle spindle and GTO loss on locomotor kinematics over two months.

Methods

We acutely eliminated muscle spindles and GTO by diphtheria toxin (DT) administration in 15 transgenic adult mice (PV^{cre};$Rx3^{flpo}$;$Mapt^{dsDTR}$;Ai65D, 9 female, 55 ± 3 day old and 22.7 ± 2.4 g on the first experimental day) expressing the human DT receptor. The animals were divided into three groups and monitored over three, seven or 60 days, and then sacrificed for histological analysis. Mice were placed on a treadmill and tested at five different speeds (0.1, 0.3, 0.5, 0.7, and 0.9 m/s). Sagittal, dorsal, and ventral high-speed videos were taken with a single high-speed camera acquiring at 250 Hz. Markerless motion capture of 74 body landmarks was obtained using DeepLabCut v2.3.9 [8]. Over 100 kinematics parameters were then calculated using custom R scripts and projected onto a low-dimensional space using principal component analysis (PCA). Where relevant, we fitted mixed effects statistical models including fixed and random (intercept varying by animal) effects.

Results and Discussion

In wild-type controls, there was no change in body mass over one week. In DT-treated animals, there was a marked loss of body mass which peaked three to four days after DT injection (DT3-DT4). Recovery of body mass was resumed by DT15 and continued until DT60. Most mice (~84%) were able to maintain fast locomotion (0.9 m/s) prior to ablation, but this ability was progressively impaired until DT3 (n = 10) and was not recovered by DT7 (n = 10) or DT60 (n = 4). PCA revealed a clear separation between kinematic parameters at DT0 and up to DT60. Paw drag and centre of mass height were among the main factors contributing to the separation in the low dimensional space of the principal components. Paw drag, where lower values indicate greater hindpaw drag during swing and thus greater impairment, showed a progressive decline within the first few days after ablation, reaching a minimum around DT3 and then plateauing until DT60. Similar trends were observed for other kinematic parameters, showing how locomotor function progressively deteriorated after ablation, peaking around 72 h after DT injection and never recovering spontaneously over the following two months. Histological analysis confirmed the temporal dynamics of proprioceptor ablation: dorsal root ganglia imaging showed progressive ablation with a maximum three days after DT injection, scaling with the motor deficits.

Conclusions

Our results show that the degree of proprioceptive loss scaled with motor impairment and that acute proprioceptive deprivation leads to rapid and persistent locomotor deficits. No spontaneous recovery of locomotor performance was observed up to two months after ablation, suggesting that the proprioceptive sensory system alone does not appear to sustain recovery through mechanisms such as sensory reweighting. This research paves the way for the development of new rehabilitation strategies, next generation neuroprosthetics and adaptive robotic systems to improve the quality of life of patients with sensory impairments.

References

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