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Circuit interrogation of whole brain reveals a novel neuromodulatory target to improve locomotion after traumatic spinal cord injury

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Objectives
Traumatic spinal cord injury (SCI) is a devastating condition that has few therapies to robustly improve neurologic function. More recently, the use of neuromodulatory strategies has shown promise including spinal epidural electrical stimulation (EES) to activate lumbar spinal circuits and leg movement. However, our understanding of the brain's role in locomotion post-SCI remains poor with a paucity of therapies despite the effectiveness of brain modulation in other motor disorders such as Parkinson's disease. The objective of this study was to understand how brain circuits change post-SCI as a means to identifying novel modulation targets to augment locomotion post-SCI.

Method
We established an unbiased mouse brain interrogation pipeline including whole brain immunolabelling, clearing, imaging, atlas registration, and cell quantification post-SCI. In mice that underwent thoracic lateral hemisection, which robustly spontaneously recover leg function, we examined changes in whole brain cFos immunolabelling and rabies-mediated projection labelling to the lumbar cord to identify a brain region whose cell activity (cFos) and lumbar cord projections (rabies) correlated with recovery. We examined this region's functional role using optogenetics and chemogenetics. To assess therapeutic translatability, we then examined electrical deep brain stimulation (DBS) of this region in a more clinically relevant rat contusion model of SCI using a customized bipedal robotic interface.

Results
Unexpectedly, the lateral hypothalamus (LH) demonstrated dynamic activity and connectivity changes correlating with mouse recovery post-SCI. Mouse LH-Vglut2 neuronal optogenetic stimulation robustly improved locomotor function, and this effect was relayed via the brainstem medullary reticular formation (MRF). Consistent with sparing of MRF projections past contusion SCI, LH DBS robustly augmented rat bipedal locomotion after contusion SCI.

Conclusions
The LH is a novel DBS target whose stimulation significantly improved locomotion after SCI, uncovered through a whole brain survey via a customized unbiased interrogation pipeline. This effect is dependent on LH Vglut2 neurons and brainstem relays. LH DBS may be a new therapy for humans with SCI, and its efficacy and safety require testing in clinical trials.