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# Vestibulospinal contributions to mammalian locomotion

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The basic mammalian locomotor pattern is generated by spinal circuits which must maintain enough output flexibility to sustain locomotion in an ever-changing environment. Lateral vestibulospinal tract (LVST) neurons receive multimodal sensory feedback regarding ongoing movement, as well as input from the forebrain and cerebellum, and send dense projections to multiple areas of the spinal cord. Traditionally, LVST-neurons have been implicated in the generation of reflexes that maintain upright posture, but they may also have an underappreciated role in the generation of normal locomotor movements. Here, we review anatomical data regarding the inputs, projection pathways and spinal targets of LVST-neurons and discuss evidence from both animal and human studies around their potential role in the modification of locomotor patterns in mammals.

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## Introduction

The basic mammalian locomotor pattern is generated by spinal circuits commonly referred to as a central pattern generator (CPG). However, naturalistic locomotion must be flexible enough to be sustained in an ever-changing environment. To achieve this, the nervous system constantly modifies and updates spinal motor output to the limb and body musculature based on sensory inflow [1], allowing mammals to maintain locomotion through corrections to limb or body position in response to external factors.

During locomotion, one key source of sensory feedback is provided by vestibular primary afferents. The vestibular system senses both self-generated and externally-generated changes in head rotation and acceleration via receptors in the inner ear and, when combined with neck proprioceptive signals, can be used to compute vectors of whole body movement [2–4,5••]. Vestibulospinal (VS) and reticulospinal neurons use this information to generate the motor commands that maintain balance and posture, and stabilise the position of the head and eyes [5••,6–11].

In terms of the contribution to locomotion, one VS pathway, originating in the lateral vestibular nucleus (LVN; also known as Deiters' nucleus) and giving rise to the lateral vestibulospinal tract (LVST), appears to be most notable. With a diverse array of inputs, axonal projections onto spinal circuits and step-cycle associated firing patterns, these LVST-neurons appear in prime position to influence the locomotor pattern and therefore shall be the focus of this review.

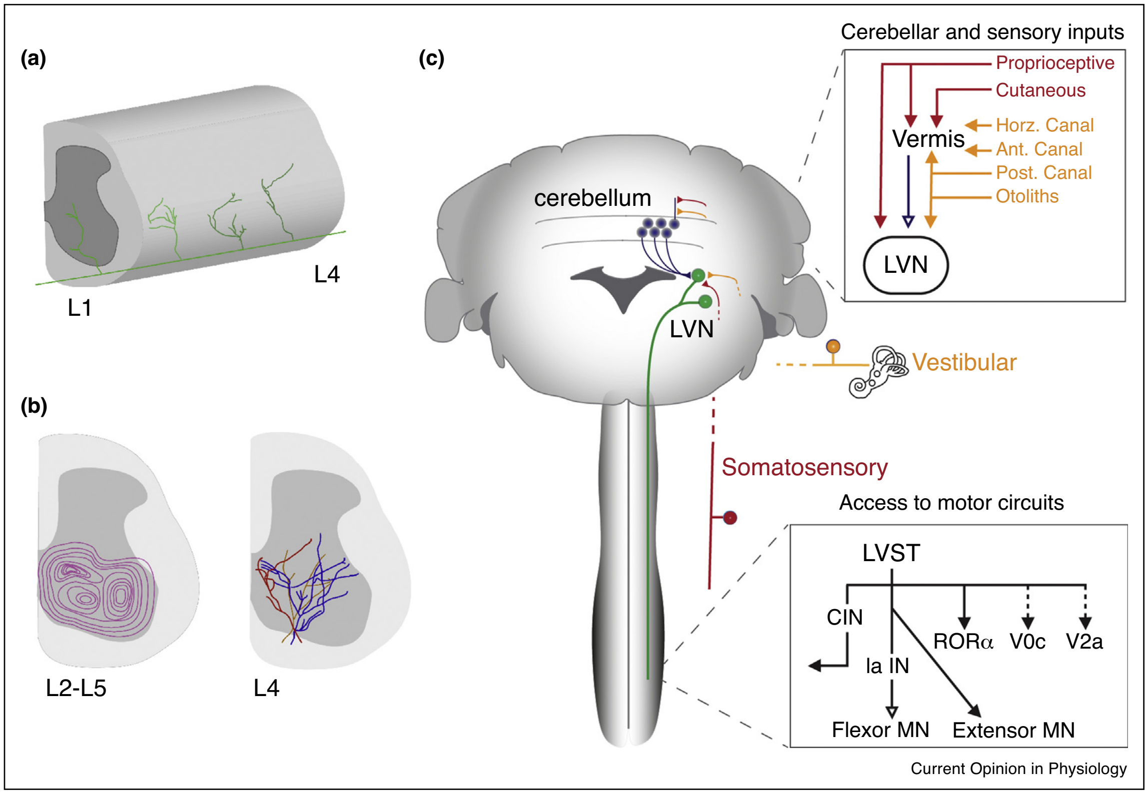
## Diverse targets of LVST-neurons suggest the ability to influence multiple musculature systems

Sherrington [12] was the first to describe a phenomenon of 'decerebrate rigidity' in cats, where extensive lesions of the forebrain resulted in extension and stiffness of the limbs, with reversal upon disruption of the LVN [13,14]. This pointed to the LVN as a modifier of extensor muscle tone, particularly to oppose gravity and maintain posture. This idea was further supported by electrophysiological studies in cats demonstrating monosynaptic excitation of motor neurons innervating extensor muscles and disynaptic inhibition of motor neurons innervating flexor muscles [15]. However, several lines of anatomical investigation suggest that control of the extensor musculature is only one aspect of LVST-neuron function.

LVST-neurons leave the LVN and send an ipsilateral, excitatory projection through the length of the spinal cord [16,17]. En route to the spinal cord, mouse LVST axons branch in the brainstem with collaterals innervating the pontine reticular nucleus, a pathway implicated in limb muscle coactivation [9]. In primates, however, LVST-neurons do not appear to have brainstem collaterals [18].

Individual LVST axons have putative synaptic contacts through large portions of the ventral spinal cord, can collateralise at several spinal levels ([19]; Figure 1a) and can innervate multiple extensor motor neuron pools [9]. In mice, LVST axons are found throughout the ventral grey matter [9,20,21], with dense projections around both the lateral and medial motor columns (the location of limb and axial motor neurons, respectively).

**Figure 1**



Branching pattern of individual LVST-neurons and integration within the locomotor system. **(a)** Branching pattern of a single LVST-axon at multiple segmental levels of the lumbar spinal cord. **(b)** Left—density plot showing position of synaptic puncta from LVST-neurons in the lumbar spinal cord. Right—overlay of four separate LVST-axons at lumbar level four. **(c)** Summary of LVST-neurons in the locomotor control system, showing sensory and cerebellar input and output to defined classes of spinal interneuron. Upper inset shows cerebellar and vestibular input to the LVN. Lower inset shows known connections between LVST-neurons and spinal interneurons. Panels A and B (right) adapted from Figure 8 in Kuze *et al.* [68]; Panel B (left) adapted from supplementary Figure 8 in Murray *et al.* [9]. Abbreviations: Ant. – Anterior; CIN – Commissural interneuron; Horz. – Horizontal; IN – Interneuron; L – Lumbar level; LVST – Lateral vestibulospinal tract; Post. – Posterior.

Dense axons are also found throughout the intermediate zone and close to the central canal ([9,20,21]; Figure 1b) and individual axon collaterals can cross to the contralateral cord [21]. This variety in branching pattern indicates that there are multiple functionally distinct populations of LVST-neurons.

LVST-neurons make synaptic contact with several classes of spinal interneuron involved in locomotion (Figure 1c). For example, commissural interneurons that connect circuits on the two sides of the spinal cord receive LVST-input, potentially allowing LVST neurons to influence motor output on both sides of the body [22,23]. In addition, LVST-axons appear in close apposition to several classes of genetically-defined spinal interneuron, including V2a and V0c [9], both of which have important roles in locomotor output [24–26]. V2a interneurons are involved in left-right alternation and are increasingly recruited into the locomotor CPG at higher speeds [25–27], whereas V0c interneurons modify motor neuron gain in a task-dependent manner [28]. LVST-neurons also directly innervate RORα interneurons, a population of dorsal premotor interneurons involved in touch sensation and fine motor control [29]. Given the extensive spinal projection of LVST axons, it seems likely that these examples represent only a fraction of their interactions with premotor circuits.

## Information processing by vestibulospinal neurons: controlled regulation of the body in space

Any modification of the ongoing locomotor pattern must respect both current body position, movement and behavioural goals. The LVN receives multimodal input from several sensory streams, as well as from higher brain areas, providing a potential means for motor output from LVST-neurons to be tuned according to the current motor state. Vestibular afferent input to the LVN is primarily from the posterior canal, which detects backwards rotation/pitch, and from the otolith organs which detect horizontal and vertical acceleration of the head [30]. The LVN also receives both direct and indirect limb proprioceptive input, and firing of some LVN neurons is modified based on current limb position and movement [31,32]. These motor feedback signals may potentially be combined with motor commands generated in higher brain regions via projections from motor and somatosensory cortices to the LVN. This includes short-latency, potentially direct, input to LVST-neurons [11,33–35].

The cerebellum represents the most prominent, and potentially most influential, input to both LVST-neurons and LVN neurons that do not directly project to the spinal cord. Purkinje cells provide a tonic inhibition onto LVST-neurons, with the majority of Purkinje cell input believed to originate from the vermal A and B zones (Figure 1c) [14]. There are also projections from both the interposed and fastigial deep cerebellar nuclei [5••]. In addition, the LVN receives collaterals from olivary climbing fibers [36] and a substantial bilateral projection from the precerebellar lateral reticular nucleus [37]. In the 1930s, Rafael Lorente de No described the LVN as a ‘chiefly cerebellar nucleus’. Given the complex interactions of the LVN and LVST-neurons with both the inputs and outputs of the cerebellum, we agree with this view and further suggest that LVST-neurons are a critical intermediary between the cerebellum and the spinal cord.

Aside from the proprioceptive, cortical and cerebellar inputs, many other regions have been reported to innervate the LVN and LVST-neurons. This includes several areas in the hypothalamus, other motor associated regions, such as red nucleus, and multiple parts of the reticular formation [38,39]. In addition, neuromodulatory input, such as that from the locus coeruleus, appears to have a prominent role in modifying the firing of LVST-neurons [40].

Although we still lack a systematic analysis of LVST-neuron inputs and outputs, it seems clear that LVST-neurons receive a diverse array of input from numerous brain regions involved in both the monitoring of current movements and the modification of forthcoming motor plans. When combined with the comprehensive spinal output pattern of LVST axons, these neurons appear well placed to contribute to some aspect of locomotor function. This brings us to the question of whether these neurons are active during locomotion.

## Activity of LVST-neurons during locomotion

In animals, LVST-neurons have been identified for *in vivo* recordings by antidromic stimulation from the spinal cord. Foundational studies by Orlovsky *et al.* [41] found LVST- neuron firing to be higher when cats were walking compared to when they were standing, with the peak of activity coincident with extensor muscle contraction. LVST-neuron activity in guinea pigs is also highest at the beginning of extensor muscle bursts [42]. Consistent with this, electrical stimulation of the LVN causes increased activity in the ankle extensor gastrocnemius lateralis with maximal increase at the start of stance phase [43]. The extensor coupling of LVST-neuron activity is absent in animals lacking a cerebellum, suggesting that the cerebellum imparts locomotor rhythm onto vestibulospinal neurons [41].

Further studies, however, have indicated that LVST-neuron firing is not a simple correlation with the actions of extensor muscles, and that multiple types of LVST-neurons can be identified based on their firing patterns. Udo *et al.* [44,45] observed two bursts of activity per step cycle in some LVST-neurons during walking. Interestingly, this double burst was only observed when all four limbs of the animal were walking, with a single burst present when only the hindlimbs were active [46]. On the basis of firing pattern, multiple classes of LVST-neuron have been proposed in cats by Matsuyama and Drew [47•]; type A which display double burst during a single step cycle, type B which are tonically active and have a single pause in activity in each step cycle and type C which have a single burst in each step cycle. Both the heterogeneity and complexity of these firing patterns suggest a role that is more nuanced than the activation of extensor muscles, and may include the coordination of all four limbs with whole body posture and movement [47•]. In addition, the amplitude (but not the overall firing pattern) of LVST-neurons is altered when cats walk on an incline, suggesting the LVST-neuron activity is involved in regulating the gain of the motor system in different environmental contexts [48].

In addition to modulation within the step cycle, the firing activity of LVST-neurons varies in a locomotor speed-dependent manner. In decerebrate cats, LVST-neurons shift from tonic, locomotor unrelated activity during slow walk to phasic, locomotor-coupled bursting during fast walk [49•]. With asynchronous hindlimb movement (i.e. during trot), increasing locomotor speed results in double-bursting of LVST-neurons, which switches to a single burst in each step cycle with symmetrical hindlimb movement (i.e. during gallop; [49•]). Together with the studies above, this appears to further corroborate a potential role of LVST-neurons in coordinating multiple limbs during locomotion.

## Inferences of LVST-neuron function by altered vestibular afferent activity

In humans and animals, LVST-neuron contribution to locomotion can be inferred either by examining subjects with a damaged peripheral vestibular system or by experimental electrical stimulation of vestibular afferents while monitoring changes in EMG and/or center of pressure.

Changes in the amplitude of coupling between vestibular stimulation and ground reaction forces suggest that vestibular information used to maintain stance is gated out to facilitate the initiation of locomotion [50•]. This presumably prevents corrective postural responses that normally act to maintain upright stance from counteracting forward movement. The relative influence of vestibular signalling during different phases of the step cycle has been investigated by initiating the stimulus at heel strike, mid-stance or toe off. Stimulation initiated at heel strike causes larger deviations in subsequent ipsilateral foot placement than stimulation initiated later in the step cycle [51], which is particularly interesting as heel strike is the critical point for planning both ongoing and future steps [52•,53]. Analogous to this are animal studies showing that LVST-neurons are also particularly active during paw placement [47•]. Vestibular-evoked muscle activity is preserved during split-belt treadmill walking, where each limb is moving at a different speed [54], suggesting that vestibular influence during locomotion can be adapted independently to each limb. When combined, these studies could point to a role for LVST-neurons in feedforward modification of locomotion, where body position and foot placement are adjusted by LVST-neurons according to behavioural goals.

As locomotor speed increases, there is a reduction of coupling between externally applied electrical vestibular stimulation and muscle activity [54,55]. This is reflected in observed as well as self-reported performance; gait deviation in response to vestibular stimulation is greater in walking than running and participants reported that walking was more difficult than running during vestibular stimulation [56]. This is paralleled by animal studies where vestibular neuropathy results in severe ataxia when walking, but a relatively normal gait while running [57,58]. Conversely, the gain of proprioceptive feedback onto spinal motor neurons appears to increase during running [59] and mice lacking proprioceptive feedback are unable to run at high speeds [60]. These observations could indicate that proprioceptive feedback is key for high speed locomotion, whereas vestibular signalling is predominant at slower speeds.

## Disruption of LVST pathways

There are currently no studies that have been able to selectively disrupt LVST-neurons while examining in detail the locomotor consequences. However, several studies have disrupted the LVN or LVST-neurons with varying degrees of specificity and looked at the consequence for certain locomotor parameters. For example, complete destruction of the LVN in cats results in the temporary disappearance of stepping movements in the ipsilateral limb, followed by weak stepping with reduced extensor activity after a recovery period of 1.5 hours [43].

Genetic disruption of vestibulospinal pathways has been achieved via the use of a HoxB1 knockout mouse line, which lacks LVST-neurons as well as some medial vestibulospinal and reticulospinal neurons [61•]. Further, viral strategies have been used to selectively ablate lumbar spinal-projecting vestibulospinal neurons [9]. Perhaps surprisingly, few gross locomotor effects were observed after genetic or viral removal of LVST neurons. This is especially remarkable given the extensive locomotor deficits found in animals with peripheral vestibular deficits [62]. However, HoxB1 knockout mice do show some subtle defects that could provide functional information. When swimming, these animals occasionally synchronously kick their hindlimbs, rather than using an alternating pattern. Similarly, when traversing a notched beam, they tend to 'hop' (i.e. synchronously activate the limbs), rather than walk between notches. When not hopping, HoxB1 knockouts also slipped off the beam more than control animals [61•]. Murray *et al.* [9] also noticed a tendency for vestibulospinal-ablated animals to take longer to traverse a square balance beam. The lack of a clear phenotype in either of these studies could be the result of a rapid compensation for disrupted vestibular pathways, as observed following LVN lesion [41] and peripheral vestibular disruption [63,64]. A clearer picture may be revealed by a combination of rapidly reversible manipulation of LVST-neuron populations and more bespoke behavioural assessments.

## Conclusion and perspectives

Like most forms of movement, locomotion has the potential to destabilise the upright position of body. Spinal motor circuits are, therefore, irreversibly intertwined with pathways that can dynamically adjust body and limb position in order to maintain an upright posture during purposeful locomotion. With direct access to both spinal interneurons and motor neurons, multimodal sensory input and locomotor modulated firing patterns, LVST-neurons appear ideally placed to make these subtle modifications. However, a lack of direct experimental assessment purely focused on LVST-neurons means that the exact role of the vestibulospinal system during locomotion remains unclear. Based on the studies above, we propose three potential areas where LVST-neurons could influence locomotor output:

1 Feedforward control of foot placement
2 Interlimb coordination
3 Speed-dependent modification of locomotor output

The cerebellum is involved in feed-forward control of locomotion and is able to modify upcoming step cycles based on a prediction of future events [65,66]. As vestibular influence on locomotion is most prominent at the point in the step cycle where ongoing and future steps are planned, LVST-neurons could provide the fast, direct route needed for the cerebellum to make modifications to locomotor output. Furthermore, the extensive sensory feedback received by the LVN from both vestibular and proprioceptive sources provides LVST-neurons with the means to implement the cerebellar plan for movement based on the current position of the body in space.

Quadrupedal animals use multiple gait types to achieve locomotion at different speeds [67]. Each gait requires the independent control of the individual limb, in coordination with the other three limbs. LVST axons have branches at both cervical and lumbar spinal levels and have extensive connections with commissural interneurons in the spinal cord [22,23], providing the required anatomical organisation for interlimb coordination. In addition, firing of LVST-neurons is modified in relation to the movement of multiple limbs, and animals lacking LVST-neurons tend to synchronously activate their hindlimbs in particular motor contexts. The nature of LVST-neuron involvement in interlimb coordination has yet to be fully explored.

Vestibular sensory feedback appears to become less influential as locomotor speed increases [49•,58]. Conversely, spinal sensory-motor feedback is increased in running compared to walking, and mice lacking proprioceptive feedback cannot run at high speeds [59,60]. The activity of LVST-neurons increases with locomotor speed [49•] and, although located in the vestibular nuclei, LVST-neurons also receive abundant proprioceptive feedback. For this reason, it is interesting to consider whether LVST-neurons themselves have differential effects on locomotion at low versus high speeds, or whether the sensory modality that drives LVST-neurons switches between locomotor speeds.

Technical challenges in both humans and animals continue to be the major hurdle in our ability to assign the specific contributions of LVST-neurons to locomotion. Future studies that can selectively target and modify the activity of LVST-neurons in awake behaving animals, combined with targeted behavioural tests, may provide a means to investigate some of the functional inferences outlined here.

## Conflict of interest statement

Nothing declared.

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