Biologically-Constrained Spiking Neural Network for Neuromodulation in Locomotor Recovery after Spinal Cord Injury

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Presynaptic inhibition after spinal cord injury (SCI) has been hypothesised to disproportionately affect flexion reflex loops in locomotor spinal circuitry. Reducing gamma-aminobutyric acid (GABA) inhibitory activity increases the excitation of flexion circuits, restoring muscle activation, and stepping ability. Conversely, nociceptive sensitisation and muscular spasticity can emerge from insufficient GABAergic inhibition. To investigate the effects of neuromodulation and proprioceptive sensory afferents in the spinal cord, a biologically constrained spiking neural network (SNN) was developed. The network describes the flexor motoneuron (MN) reflex loop with inputs from ipsilateral Ia- and II-fibres and tonically firing interneurons. The model was tuned to a baseline level of locomotive activity before simulating an inhibitory-dominant and body-weight supported (BWS) SCI state. Electrical stimulation (ES) and serotonergic agonists were simulated by the excitation of dorsal fibres and reduced conductance in excitatory neurons. ES was applied across all afferent fibres without phase- or muscle-specific protocols. The present study describes, for the first time, the release of GABAergic inhibition on flexor MNs as a potential mechanism underlying BWS treadmill training. The results demonstrate the synaptic mechanisms by which neuromodulatory therapy tunes the excitation and inhibition of ankle flexor MNs during locomotion for smoother and more coordinated movement.

spiking neural networks | neuromodulation | spinal cord injury | locomotion | computational neuroscience

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Introduction

SCI globally affects an estimated 9 million people as of 2019, with an age standardised incident rate of about 109 per 100,000 (1). In the event of SCI, damage to nervous tissue can result in loss of voluntary control, sensation, spasticity, diaphragm dysfunction, pressure ulcers, and pain syndromes (2, 3). Sufferers of SCI often report non-physical symptoms such as emotional disorders, loss of independence, depression, anxiety, and clinical levels of stress (4). The lifelong management places intense financial burden not only the patients and their communities but also on the broader economic landscape (5, 6). Lifetime medical costs in Canada can range from $1.47 to $3 million CAD (2013 prices) per person (7), £1.12 million per person in the UK (2016 prices) (8), and range from $0.77 to $1.3 million USD (1995 prices) in the US (9). Recovering voluntary muscle activity and returning locomotion activity to SCI sufferers could save societal and patient costs while also improving the patient's quality of life (10, 11).

Recovering gait remains as a top priority for people living with SCI (12). Flexor activity is critical for step progression during locomotion, acting as shock absorbers before foot strike (13), adapting step-height to continue locomotion progression (14), and resetting locomotion (15). Increasing excitability of locomotor networks after paralysis can improve locomotor capabilities however, hyperexcitation of flexor muscles can result in spastic muscle expression, leading to poor balance and coordination (16–18). Maintaining an excitation-inhibition balance of excitability emerges as an intuitive solution to enabling robust locomotor expression.

SCI interrupts normal bidirectional signalling, leading to dysfunctional neural circuitry, tilting the balance of excitation and inhibition (19). Lack of descending activity keep MNs at a predominantly inhibited state while inhibitory populations in the dorsal and intermediate zone become over-reactive (20, 21). A large percentage of the SCI population experience spastic muscle activity, likely due to insufficient release of GABA neurotransmitters (22–26). Nevertheless, even with an overly excited or inhibited environment and detached from brain inputs, the locomotor spinal circuit can continue to express coordinated motor function given sufficient excitation and contextually relevant sensory information (27–31).

Proprioception is a critical sensory input to entrain and recover locomotion after SCI (32–34). Proprioceptive afferent innervation is widespread and diverse, projecting to MNs (35–37), GABAergic (38, 39), and serotonergic (40–43) interneurons (INs) in the dorsal and intermediate zone of the spinal cord. Long and short axons spread across multiple segments and organised spatially and by modality (37, 44–46). Proprioceptive interneurons (PINs) are mainly excitatory, with most inhibitory populations projecting ipsilaterally (47). Due to their complex and integratory nature, PINs have been suggested to be a possible neural detour around spinal lesions, recovering voluntary sensorimotor control after SCI (46, 48–51).

After SCI, axons spared from injury allow voluntary activation and sensation of the body past lesion sites (51, 52). Traditional rehabilitation therapy leverages these residual connections to maximise motor skills via therapeutic exercise or overcome losses with assistive devises (28, 53). Neuromodulation techniques such as spinal cord ES (30, 31, 54, 55) and

pharmacology (51, 56, 57) have shown to recover locomotor activity after SCI. Moreover, chronic application of ES in conjunction with physical rehabilitation enabled volitional muscle activation even without ES (29). Although these observations show promise for new and effective neurorehabilitation therapies, the mechanisms of action and synergy between sensory ensembles and ES remain in question (58, 59). It is natural to seek methods to return excitation to sublesional networks after losing descending input (60). Most ES techniques have sought to excite and entrain locomotion by activating dorsal roots in the epidural space (59, 61–64). However, ES, in the same anatomical space, using similar stimulation protocols, can equally evoke inhibition and restore an overly excited network (23, 24, 65). A more in-depth and nuanced view of ES therapy is required to fully appreciate the complexity of modulating the neural environments. A key question remains: How do neuromodulation therapies integrate with sensory information? We hypothesise that spinal cord locomotor circuits require balanced excitation and inhibition to coordinate flexor activity.

This study describes a biologically constrained tibialis anterior (TA) SNN rodent model receiving heterogeneous excitatory and inhibitory synapses, including GABAergic presynaptic inhibition. A combination of ES and serotonin agonist (5-HT) neuromodulators are simulated in an SCI and SCI with BWS locomotion setting. We show that combining BWS with ES reduces overactive stance-evoked GABA inhibition and returns TA MN firing rates towards baseline.

Methods

A biologically constrained SNN was developed to investigate the effect of neuromodulation on sensory-driven rodent spinal locomotor circuits. Simulations were run on an Intel Xeon Gold 6238R 2.2GHz Processor. The software was developed in Python 3.10.0 using the Brian2 neural simulator module (v2.6.0) (66). The simulation time step was set to 5 µs and Euler approximations were used for ordinary differential equation solving. A total of 9 steps were simulated, where gait stance and swing phases were split at 65% of the gait cycle (67). This study simulated three different neurological environments, including a baseline, SCI, and SCI with a BWS state. Each neurological state was modulated with inputs from ES and 5-HT.

The SNN model architecture was biologically constrained using synaptic connections inferred from previous cell staining (39, 61, 68, 69), electrophysiological (70–76), and genetic works (77–82). A second biological constraint was set by matching neuron cell dynamics to experimentally measured electrophysiological neural recordings (62, 68, 75, 77, 78, 80, 83–85). Specific parameter settings are described in the below sections and set to be within biologically plausible ranges. Finally, propriosensory inputs were constrained to previously validated musculoskeletal and muscle spindle models (62).

The simulated data was considered dependent and tested using the Shapiro-Wilk method, where $p > 0.05$ was considered a normal distribution. Normal distributions were tested for significance using Tukey Honestly Significant Difference (HSD), and non-normal distributions were tested using the Wilcoxon signed-rank test. The distributions were considered significantly different if $p < 0.05$. Population firing rates were averaged with a 25 ms Gaussian window. Experiment code can be found at https://github.com/rchia16/balancing-locomotor-networks.git.

Afferent Signal Inputs. Ia and II TA and gastrocnemius medialis (GM) muscle afferent signals were calculated by using musculoskeletal and muscle spindle models during locomotion, described in previously validated computational models (62). To emulate BWS afferent signals, both TA and GM Ia and II data were offset by a scalar amount using values from electrophysiological experiments (86). The new BWS equations were set to equations (1) and (2) where $K_{GM} = -0.6$ and $K_{TA} = -0.122$, scaling the EMG envelope to 40% and 87.8% respectively, simulating 60% effective body weight. The equations refer to x as stretch, v as stretch velocity, and EMG_{env} as the min-max normalised EMG envelope (87). Since EMG_{env} magnitude ranged between 0 and 1, a scalar offset can be applied to the afferent signal inputs (62). Afferent signals were set as timed array poisson distributed inputs with a sampling frequency of 200 Hz and connected to leaky integrate and fire (LIF) axon models, see equation (3) and Fig. 1 A and B. Parameters were set according to previously validated computational models (61) and tuned to replicate the input firing rate, see table 1. Tuning was validated with Pearson correlation coefficient and mean absolute error, refer to table 5.

$$\text{Ia firing rate} = 50 + 2 \cdot x + 4.3 \cdot sign(v) \cdot |v|^{0.6} + K \cdot 50 \cdot EMG_{env} \quad (1)$$

$$\text{II firing rate} = 80 + 13.5 \cdot x + K \cdot 20 \cdot EMG_{env} \quad (2)$$

$$\frac{dv}{dt} = \frac{E_l - v}{\tau} \quad (3)$$

Table 1. Afferent axon parameters for LIF model.

Parameter	Value
N	60
τ	30 ms
$\tau_{refractory}$	1.6 ms
E_l	−80 mV
V_{th}	−60 mV
V_{rest}	−70 mV

Spiking Neural Network. The SNN model simulated ipsilateral rodent ankle flexor's mono- and di-synaptic stretch and stretch velocity afferent reflexes. Proprioceptive afferents innervated the TA MN, GABA, Ia inhibitory, and V2a interneurons (88, 89). Ia inhibitory interneurons (IaINs) receiving Ia and II afferent inputs of the flexor and extensor muscles were reciprocally inhibited (79). GABA INs applied presynaptic inhibition to excitatory inputs of the TA MN (69, 90).

V2a INs received flexor II afferent inputs and applied tonic excitation to TA MNs (77, 91). TA MNs received monosynaptic excitation from flexor Ia afferents (81, 92). Refer to Fig. 1 A for an illustration of the entire network and figures 9 and 10 for tonic bursting neural firing.

IaINs were modelled as conductance-based LIF neurons receiving excitation from Ia and II afferent fibres and inhibition from opposing IaINs, see equation (4). I_{syn} is the cumulative synaptic current from excitatory and inhibitory components. IaIN parameters in table 2 were set to match experimental results (62, 68).

$$\frac{dv}{dt} = \frac{g_L(E_L - v) + I_{syn}}{C_m} \tag{4}$$

Table 2. Ia inhibitory, GABA, V2a IN and MN parameters.

Parameter	IaIN	GABA	V2a	MN
N	196	196	196	169
C_m	31.13 pF	100 pF	45 pF	162 pF
E_L	−70 mV	−70 mV	−53 mV	−70 mV
V_{th}	−50 mV	−50 mV	−42 mV	−50 mV
V_{rest}	−65 mV	−62.3 mV	−47 mV	−65 mV
g_L	5 nS	1.2 nS	1.2 nS	27 nS
Δ_v	–	2 mV	0.5 mV	0.05 mV
a	–	2 nS	2 nS	–
τ_w	–	20 ms	55 ms	–

GABA presynaptic inhibitory INs and V2a INs were modelled as conductance-based adaptive exponential (AdEx) LIFs (84). GABA parameters (80, 83) and V2a parameters (75, 77, 78) were set as per experimental results. AdEx equation was defined per equation (5). GABA and V2a IN parameters were set per table 2. V2a IN g_L was reduced by 40% during SCI experiments and 15% during BWS experiments (85).

$$\frac{dv}{dt} = \frac{g_L(E_L - v) + g_L(\Delta_v \exp\frac{v - v_{th}}{\Delta_v}) + I_{syn} - w}{C_m} \tag{5}$$

$$\frac{dw}{dt} = \frac{a(v - E_L) - w}{\tau_w} \tag{6}$$

TA flexor MNs were modelled as exponential LIFs receiving excitation from TA Ia fibres, V2a INs, inhibition from GM originating IaINs and presynaptic inhibition from GABA INs (38, 62, 93). The equation for TA MNs was the same as equation (5) where $w = 0$. Parameters in table 2 were set to best estimate experimental results (68, 94, 95). To simulate serotonin agonist response, MN g_L was reduced by 40% during SCI experiments and 15% during BWS experiments (62, 85, 96). See Fig. 9 for MN responses with varying stimulation pulse widths.

Synapses. Alpha and exponential conductance synapses were used to describe inhibitory and excitatory synapses, respectively, see table 3 and Fig. 1 D and E. The reversal potential of excitatory synapses was set to 0 mV, while inhibitory synapses were set to the target neuron reverse potential. II-fibre synapse weights were scaled by a factor of 0.33 to simulate the effect of smaller axon size (62, 97).

Synaptic connections, with the exclusion of GABA, were determined by probabilities specified in table 4. Axon synapses included a 2±0.3 ms delay accounting for diameter variability (98). GABA connections were predetermined by index rules dependent on the experiment condition; see Fig. 1 C. GABA connections were tuned to match previous baseline responses (59, 62). SCI condition GABA connections were increased by 160% as seen in flexor MNs after SCI transection (69).

Presynaptic inhibition was a multiplicative gain, scaling synaptic weights of each excitatory connection to the TA MN population (72, 80, 99, 100). GABA spillover was modelled as a linear decrease in release factor, p, see equation (7). β determined the strength of the inhibition and set to a value of 0.4. C_{GABA} was considered a unitless value for local GABA concentration (101).

$$\tau_p \frac{dp}{dt} = -p + (1 - \beta \cdot C_{GABA}) \tag{7}$$

Table 3. Alpha and exponential synapse and GABA spillover parameters. Alpha synapses were used for inhibitory connections while exponential synapses were used for excitatory connections.

Parameter	Value
τ_{exc}	0.25 ms
$\tau_{inh,rise}$	2 ms
$\tau_{inh,decay}$	4.5 ms
τ_p	20 ms

Table 4. Synapse connection probabilities (p) and synaptic conductance by source and target neurons. Excitatory (exc.) and inhibitory (inh.) synaptic conductance apply to target neurons.

Source	Target	p	Exc.	Inh.
Axon	IaIN	0.3	7 nS	–
Axon	GABA	0.4	12 nS	–
Axon	V2a	0.6	1 nS	–
$\text{IaIN}_{TA/GM}$	$\text{IaIN}_{TA/GM}$	0.1	–	3 nS
Axon, V2a, IaIN	MN	0.3	30 nS	10 nS

Poisson distributed neural groups simulated subthreshold stimulation with user-specified input rates. Each stimulation input was connected to three afferent fibres (Fig. 1C). To validate the SNN model, an EMG signal (Fig. 1F) was generated using convolutions of representative motor unit action potentials using the same parameters as experimental and previously validated computational models (59, 102).

Results

A spinal reflex recruitment protocol validated the interactions between neural groups, synapses, and ES and afferent axons in a static environment. Early- (ER), middle- (MR), and late-response (LR) latencies were defined as 1 ms, 4 ms, and 7 ms respectively (106). The protocol was adapted from previous

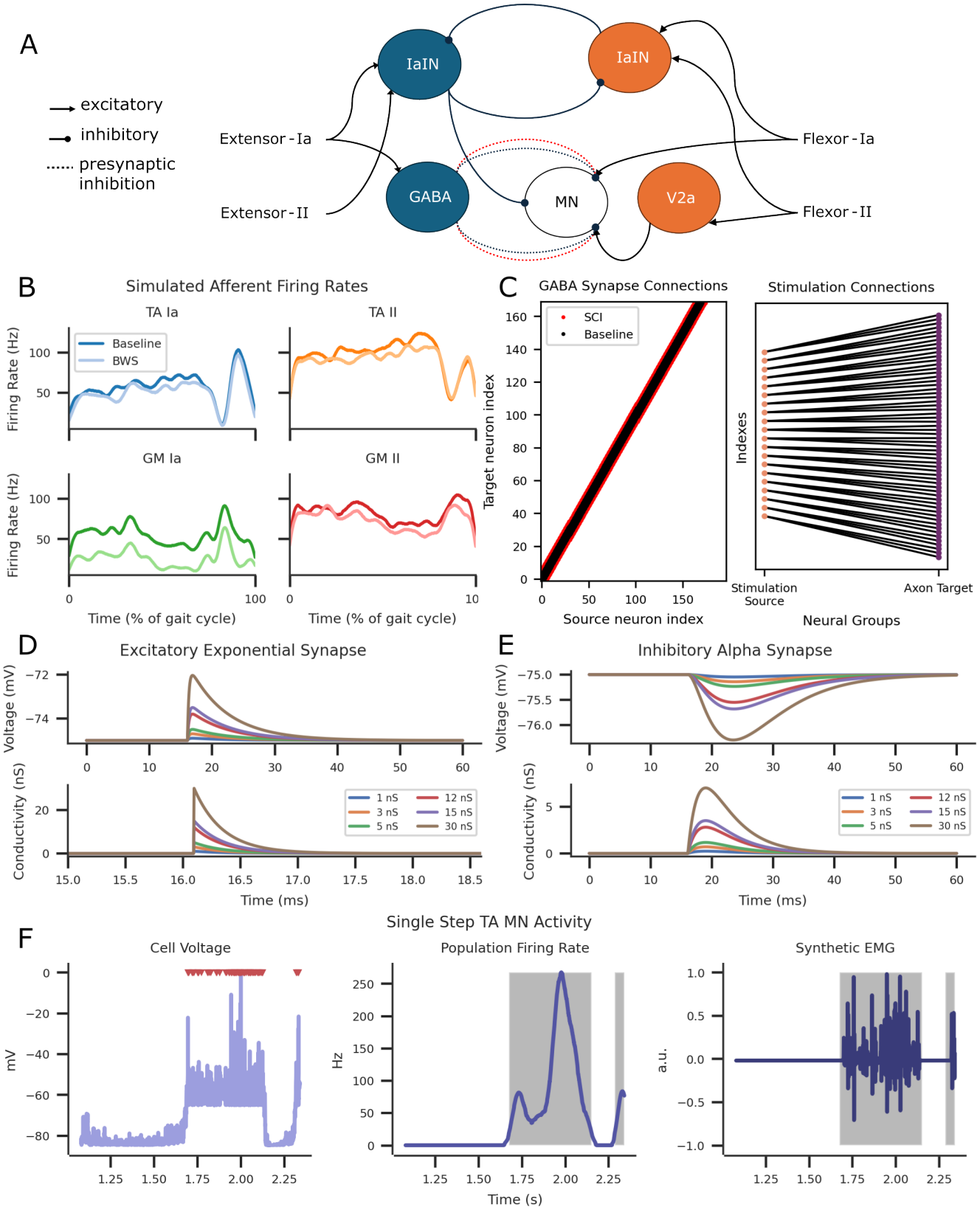

Fig. 1. Computational SNN model of the flexor network with GM extensor and TA flexor proprioceptive Ia and II inputs. **A** Biologically constrained SNN ankle flexor model. Arrow ends indicate excitation, circle ends indicate inhibition, and dotted line with circle ends indicate presynaptic inhibition connections. The red dotted lines represent increased SCI induced GABA synapses. **B** Afferent axon firing rates for extensor (GM) and flexor (TA) Ia- and II-fibres in the baseline and BWS condition. **C** GABA synapse connections (left) between the source and target neuron in the Baseline and SCI condition. Poisson stimulation input to afferent axon connections (right) during ES condition. SCI synapses retained the Baseline connections with the addition of the synapses depicted in red. **D** Excitatory exponential synapses and **E** inhibitory alpha synapses across different conductances. **F** Simulated TA MN output from a single step. Left illustrates the MN extracellular voltage activity with spiking activity indicated with red triangles. The firing rates were converted into $25\,\mathrm{ms}$ window widths and smoothened with a gaussian filter (middle). Synthetic EMG activity was generated from recorded spiking activity by convolving gaussian wavelets (right). Grey shading highlights detected bursts of firing rate activity.

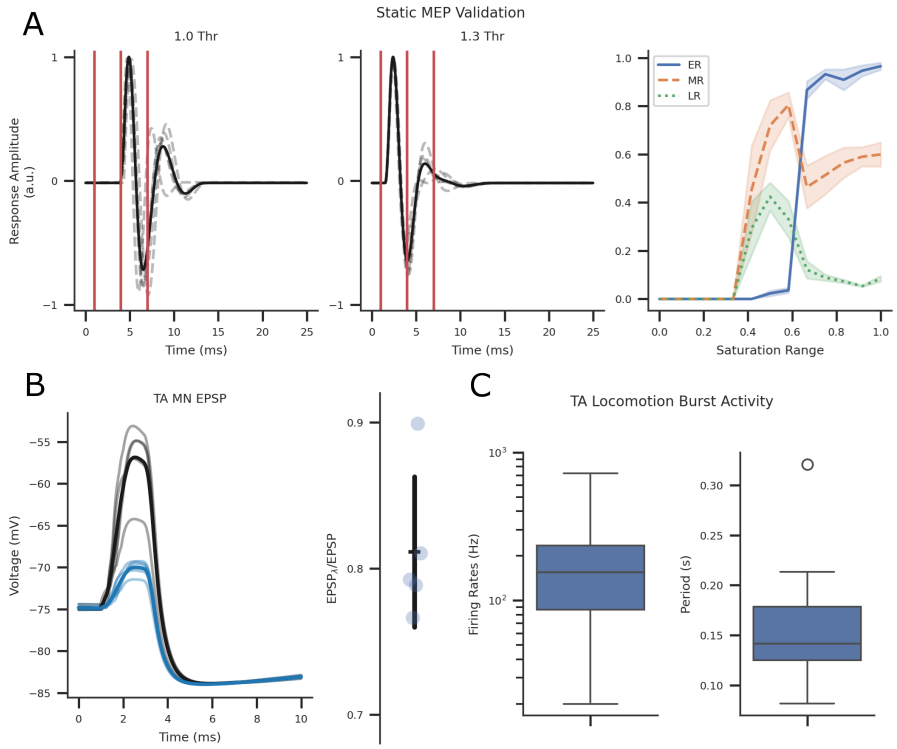

Fig. 2. Static (n = 5) and dynamic (n = 9) qualitative and quantitative validation of the SNN model. **A** Motor evoked potentials (MEPs) at stimulation intensities ranging from 0 – $600\,\mu\mathrm{A}$ and $0.5\,\mathrm{ms}$ pulse width with $1\,\mathrm{s}$ between each pulse (59, 103). Results qualitatively match reported findings. **B** Modulation of excitatory post-synaptic potential in control (black trace) and GABA IN stimulation (blue trace) experiments. Fifteen $1\,\mathrm{ms}$ pulses at $50\,\mathrm{Hz}$ with a $45\,\mathrm{ms}$ delay stimulated GABA INs before delivering afferent fibre stimulation at 1.1x threshold (80). The ratio of maximum peaks was within the range of experimental results. **C** TA burst firing rates and periods during baseline locomotion were within the the range of experimental results. (104, 105).

animal and simulation experiments and qualitatively assessed the SNN model validity (59, 103). The shape, latency, and modultation of evoked responses were qualitatively comparable to in-vivo measurements (Fig. 2A). Increased stimulation intensities led to the recruitment of efferent fibres, suppressing MR and LR amplitudes, matching previously reported simulations and experimental data.

Additionally, GABA interaction validation was performed by adopting electrophysiological evoked response experiments in intracellular recordings of the TA MN (Fig. 2B). To simulate the photostimulation of GABA neurons, a threshold current pulse was injected using the same pulse durations, frequencies, and delays from experimental protocols (80). The ratio of extracellular potential during control and photostimulation conditions was within range of experimental results.

The SNN model was further verified within a dynamic setting (Fig. 2C) using previously validated afferent fibre firing rate profiles during locomotion (62). The MN firing rates were recorded and processed with the same window size ($4\,\mathrm{ms}$) as experimental methods in rodents and validated by comparing TA MN burst firing rates and periods during locomotion (104, 105). The burst activity during locomotion fell within the range reported in experimental data.

Statistical analysis on flexor activity after outlier removal (SCI, $\mathrm{SCI}_{\text{5-HT+ES}}$) during each phase presented a non-normal distribution in the swing and stance phases ($p < 0.05$). Swing phase flexor activity significantly differed between all simulated conditions with the exclusion of baseline – $\mathrm{BWS}_{\text{5-HT+ES}}$

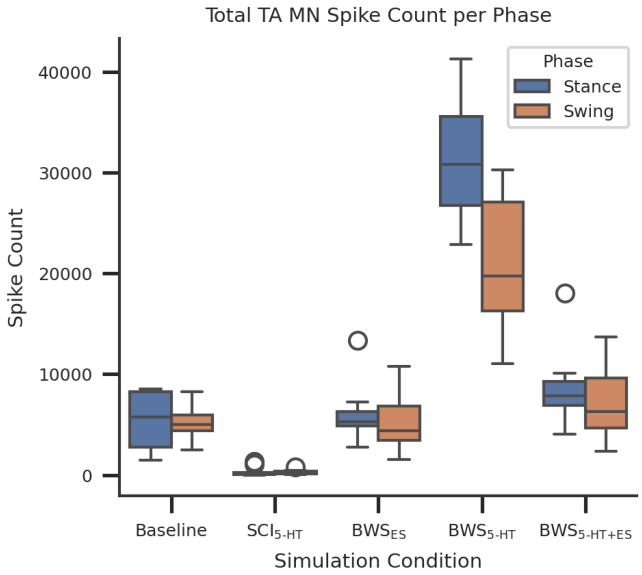

Fig. 3. Box-and-whisker plots of 9-steps during baseline and simulated conditions. All swing flexor activity was non-normal and significantly different with the exception of Baseline to BWS_{ES} and $\mathrm{BWS}_{\text{5-HT+ES}}$. All stance flexor activity was significantly different with the exception of Baseline to BWS_{ES}.

and BWS_{ES} pairs. Stance phase flexor activity was significantly different in all simulated conditions except baseline – BWS_{ES} pairs. See Fig. 3 for TA MN activity distributions in both swing and stance phases. Box-and-whisker plots for GABA INs and V2a INs can be found in figures 11 and 12. Simulated TA MN expression during baseline step cycles was

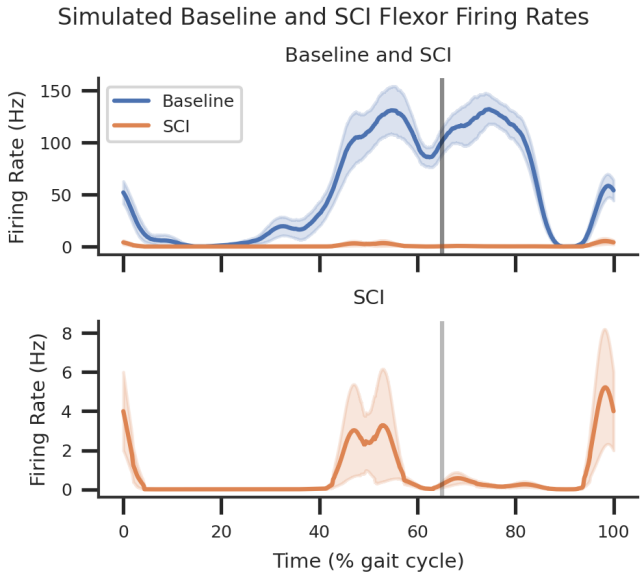

Fig. 4. Average and standard deviation plots of 9-steps during baseline and simulated SCI conditions. The vertical grey line separates the stance (left of the grey line) and the swing (right of the grey line) phases, estimated at 65% of the gait cycle (67).

unaffected by stimulation amplitudes but minorly affected by frequencies, refer to Fig. 5. Though, GABA and V2a INs firing rates were scaled according to stimulation frequency. Note $20\,\mathrm{Hz}$ and $40\,\mathrm{Hz}$ at $10\,\mathrm{mV}$ stimulation intensities resulted in the same firing patterns.

During baseline stepping, most variation occurred within the swing stages and transition between the swing and stance phases of the gait cycle, see Fig. 4. The TA MN population firing rates between baseline and SCI conditions were significantly different. Deterministically scaling the GABAergic connectivity to flexor MNs by 1.6 reduced mean firing rates by $53.6\,\mathrm{Hz}$ and increased the coefficient of variation by a factor of 9.2.

While the GABA IN firing rates were the same between simulated baseline and SCI settings, increased GABAergic connections resulted in more frequent presynaptic inhibition activity on TA MN populations (Fig. 3). GABA IN firing rates were increased while receiving ES inputs. V2a IN firing rates were equal between baseline and SCI since it did not receive GABA IN synapses. Simulating SCI serotonergic agonist activity by reducing the membrane conductance of V2a INs and MNs only slightly increased firing rates in MNs. This effect was abolished when combined with ES, see figures 3 and 6. Applying 5-HT+ES increased V2a IN and GABA IN activation, reducing the MN excitation to below SCI. In combination with the SCI condition, ES resulted in the same MN firing rate expression as 5-HT+ES.

BWS locomotion with SCI increased overall flexor activity to averages greater than the baseline condition. This was further amplified with the introduction of 5-HT. Applying ES without 5-HT smoothened the output of MN activity, returning MN activations to baseline. Combining 5-HT and ES further increased peak activity during the swing phase and reduced activations during stance phases, see figures 3 and 7.

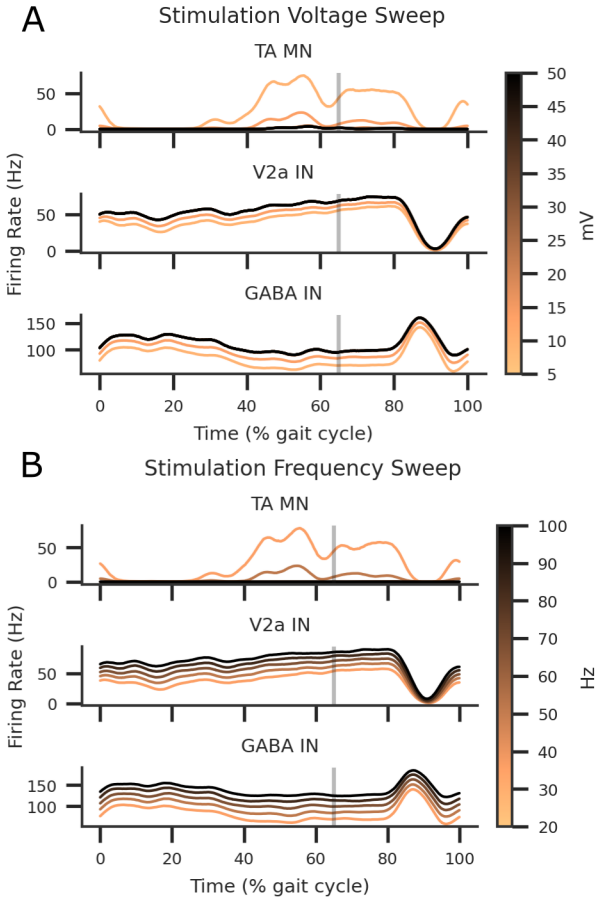

Fig. 5. ES intensity and frequency sweeps using poisson inputs to flexor and extensor afferent axons. **A** Stimulation intensity sweep applied at 5, 10, 20, 30, 40, and $50\,\mathrm{mV}$ at a $40\,\mathrm{Hz}$ frequency. **B** Stimulation frequency sweep applied at 20, 40, 60, 80, and $100\,\mathrm{Hz}$ at $10\,\mathrm{mV}$ amplitude.

The reduction in flexor afferents from BWS reduced the 5-HT-modulated V2a IN activity towards SCI levels; these effects were reversed with ES modulation. GABA IN activity was reduced due to BWS simulated stance EMG reduction. Introducing ES returned GABA IN activity closer to the baseline. GABA activity was equivalent when comparing $\mathrm{BWS_{ES}}$ and $\mathrm{BWS_{5\text{-}HT+ES}}$ since no modulation was applied from serotonin, refer to figures 3 and 7.

Discussion

A biologically constrained SNN model of the flexor reflex circuit was designed to investigate the integrative mechanisms between sensory and neuromodulation inputs to the spinal cord. Analysis of the stance and swing phases of 9 steps during simulated SCI activity revealed serotonergic agonists as a method to excite V2a INs and TA MNs after SCI. Applying unspecific ES to proprioceptive afferent axons amplified the effects of reciprocal inhibition, further accentuating excitatory peaks and inhibitory valleys. Moreover, simulating BWS locomotion decreased presynaptic inhibition, which reestablished TA MN firing rates. Applying ES during BWS locomotion resulted in a smoother MN activation profile, returning swing and stance firing rates to the baseline level.

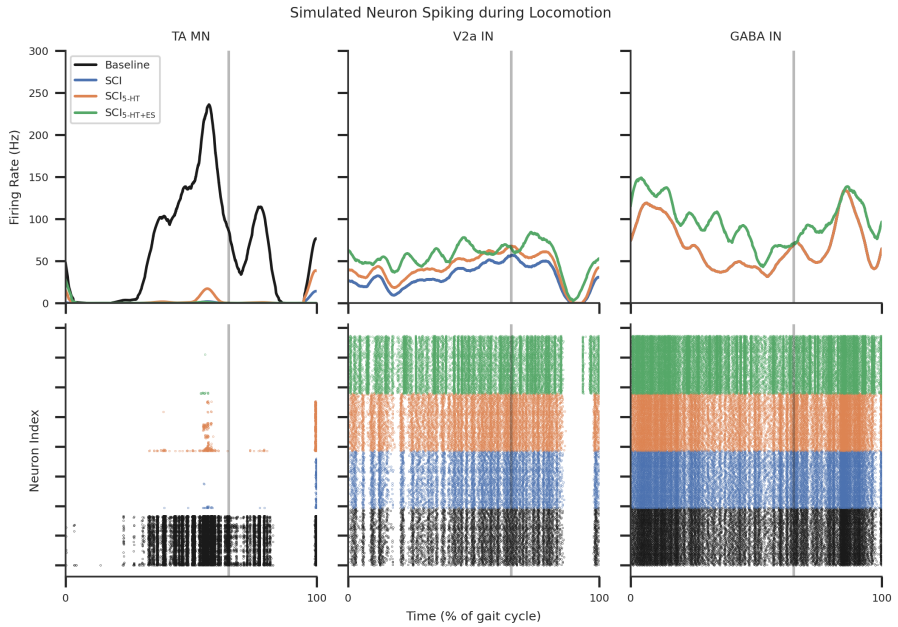

Fig. 6. MN, V2a IN, and GABA IN spiking activity during an example step. The effect of SCI and SCI while receiving serotonergic agonists, (5-HT), and the combination of 5-HT and ES (5-HT+ES) were compared. The top row illustrates the population firing rates and the bottom row shows the individual neuron spiking activity during the gait cycle.

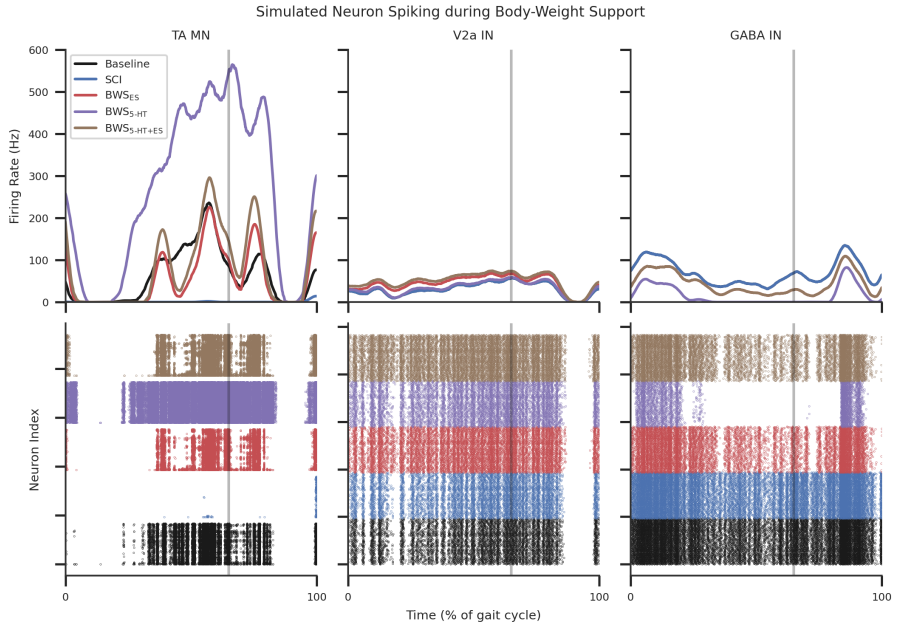

Fig. 7. MN, V2a IN, and GABA IN spiking activity during an example step during simulated BWS locomotion. The effect of BWs while receiving serotonergic agonists (5-HT) and the combination of 5-HT and ES (5-HT+ES) were compared. The top row illustrates the population firing rates and the bottom row shows the individual neuron spiking activity during the gait cycle. Descreased firing rates from extensor afferents increased excitation in V2a INs and MNs by reducing the effect of inhibition.

Historically, ES has been applied for chronic pain management and spasticity reduction (65, 107, 108). The activation pathways of spinal cord stimulation for pain management are understood to be via large-diameter dorsal column and root fibres that carry propriosensory, mechanosensory, and nociceptive information (109). GABA INs activate and depress afferent nociceptive signals by antidromic activation of the dorsal column at frequencies, electrode positions, and stimulation amplitudes similar to that of ES for sensorimotor recovery (110, 111). Similarly, ES applied for spasticity reduces the excitatory inputs to MNs through the proprioceptive inhibitory pathways (112, 113). Yet, literature in SCI motor recovery places an intense focus on excitation (31, 114, 115).

Given the heightened inhibitory state of the injured spinal cord, it seems intuitive to return excitation to depressed neurons. However, results from this study suggest activating the spinal cord with the same proposed mechanisms as pain and spasticity modulation equally activate inhibitory pathways, strengthening an already maladapted inhibition dominant circuit (69, 116). A more refined and nuanced approach needs to be considered in order to return the required balance of ex-

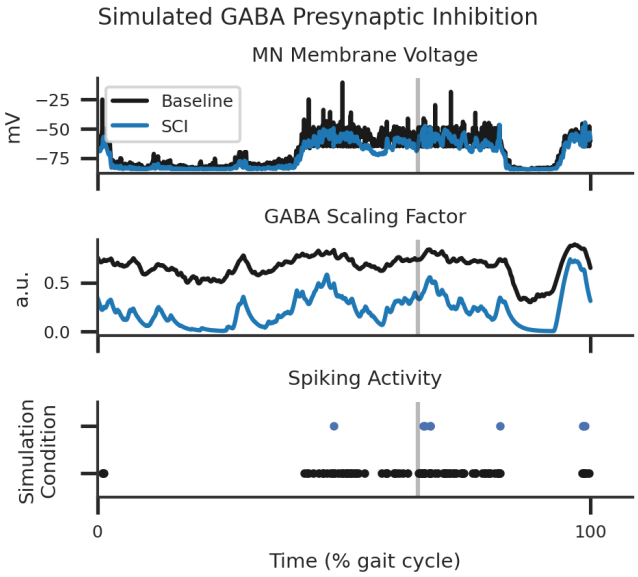

Fig. 8. SCI simulation of a single motoneuron receiving presynaptic inhibition by local concentration of GABA transmitters during a single step. Note the reduced number of spike events due to GABA inhibition.

citation and inhibition to allow phasic activity to propagate. Results in this study suggest that appropriate sensory information must be provided to drive flexor network plastic adaptation towards a less inhibited and more task-specific tuned state. Tonically depressing or exciting, the spinal circuits do not provide the necessary sensory information to provide that plastic tuning (117, 118). This explains the requirement of propriosensory information for locomotor recovery after SCI (32–34).

The normal sensory processing occurring within the injured spinal cord becomes more stochastic and lacks the necessary bias required to perform the task (106). As a result, pre-motor polysynaptic connections play a more active role in the expression of muscle tone and activity (119). By establishing an appropriate balance in excitation and inhibition, repetitive sensory information can reinforce appropriate synaptic adaptations towards a more functional spinal state (60, 120). Results in this study show, for the first time, the synaptic mechanisms at which this can be accomplished and provide an understanding of why BWS treadmill training works (121–123).

The greater deviation in normalised firing rate indicates greater variation in neuronal populations after SCI (figures 4 and 8). This may be due to the lack of necessary excitation required to inhibit and excite in phase with the incoming sensory signals (106). Thus, increasing the excitability of MNs and premotor excitatory neurons and reducing the effect of stance phase inhibition by BWS can assist with reducing inhibitory effects on flexors (124–127). After reaching a suitably excitable state where phasic step information can propagate in a timely manner, sub-threshold ES could provide the necessary smoothening process to synergistically reinforce relevant pathways without too much inhibition or excitation (62, 128, 129).

Computational studies such as this are limited in their ability to generalise due to the estimates and tuning that are required to generate the model itself. The simulated flexor reflex loop's SNN architecture is simplistic compared to the complex bidirectional information exchange between the contralateral sides (130, 131). Though the cells were modelled from experimental data, there are errors and missing variables within experiments that have a carry-on effect on computational models. This study utilised LIF and AdEx equations to reduce computational burden and improve simulation runtime speeds. Though previous efforts have incorporated the same approach (59, 62), mathematical approximations of firing patterns limit the generalisability (132, 133). However, even with simple estimations, a computational model could provide new hypotheses to the inner workings of neurological systems and unlock novel recovery protocols (111, 134).

Future studies could include the experimental verification of these findings via electrophysiological or genetic ablation experiments in rodent models in BWS neuromodulated locomotion contexts. Moreover, extending the model enable investigation of previous electrophysiological results that uncovered correlations between the appearance of long-latency polysynaptic potentials and recovery of locomotion in spinal rats (35, 57, 103, 128, 135, 136). Re-emergence of uninterrupted late-response polysynaptic potentials may be the expression of increased excitability in local spinal networks, re-balancing the inhibitory dominant pre-motor circuity (106, 119). Functional recovery may be mediated by increased magnitude in polysynaptic activity, compensating for the loss in direct excitation (60). Finally, extending the computational model to include neuroplastic dynamics could uncover the relationship between neuromodulation and neuroplastic adaptations (101, 137, 138). Investigating these effects within an extended biologically constrained computational model would be worthwhile.

Conclusions

The development of a biologically constrained SNN has provided insights into the mechanistic basis of sensory and neuromodulatory integration after SCI. Simulations suggest that BWS locomotion in conjunction with ES returns phasic flexor coordination in an inhibition-dominant environment. Without BWS, serotonergic agonists increased excitation to enable sensory-driven flexor rhythmic activation. The spinal cord requires a balance of excitation and inhibition to enable the correct phasic modulation of sensorimotor pathways. The work described in this chapter provides a potential explanation for why BWS locomotor training works with neuromodulation.

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Bibliography

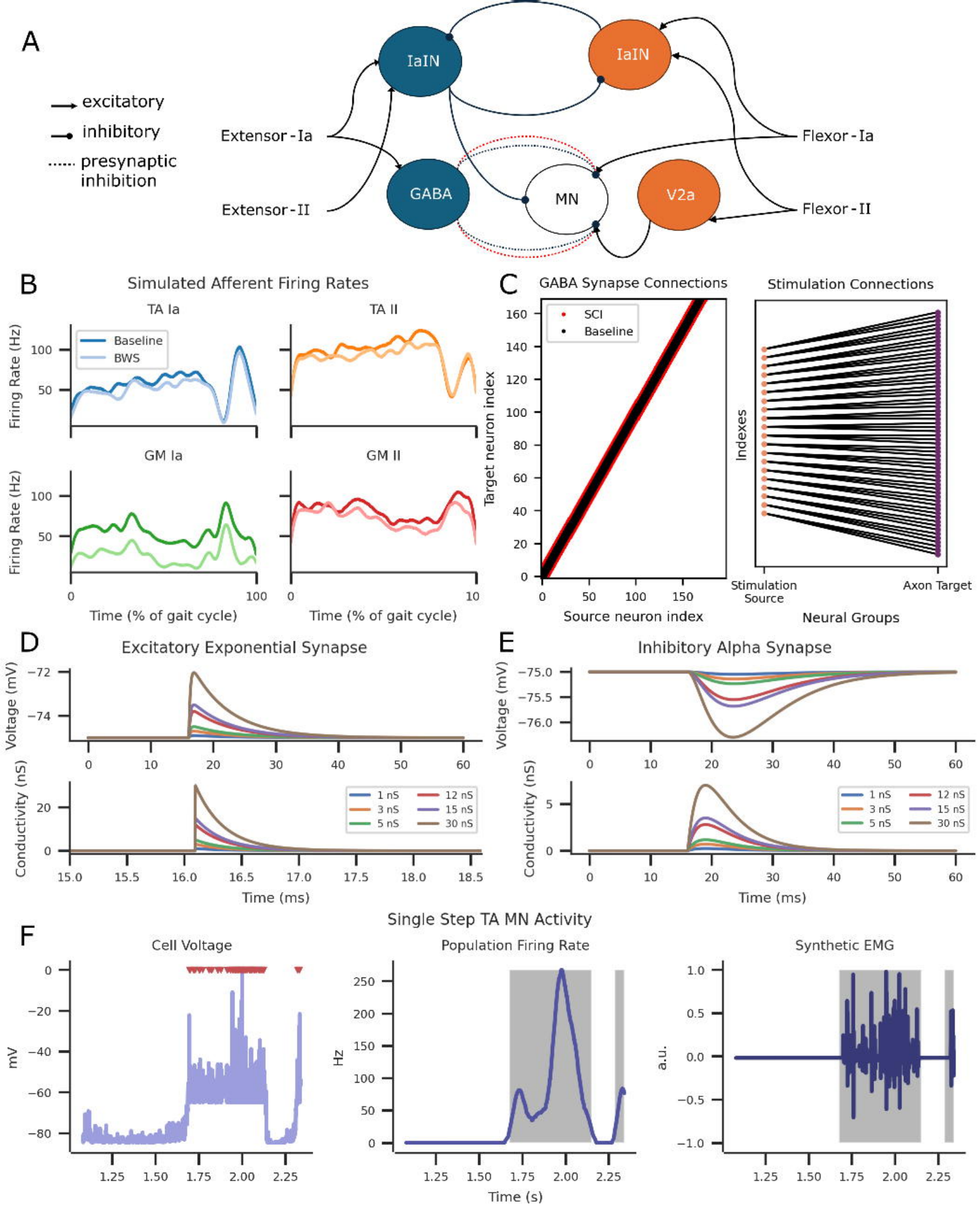
1. Yimin Dong, Renpeng Peng, Honglei Kang, Kehan Song, Qian Guo, Hongjian Zhao, Meipeng Zhu, Yayun Zhang, Hanfeng Guan, and Feng Li. Global incidence, prevalence, and disability of vertebral fractures: A systematic analysis of the global burden of disease study 2019. *The Spine Journal*, 22(5):857–868, May 2022. ISSN 1529-9430. doi: 10.1016/j.spinee.2021.12.007.
2. N. Sezer, S. Akkus, and F. G. Ugurlu. Chronic complications of spinal cord injury. *World journal of orthopedics*, 6(1):24–33, 2015. ISSN 2218-5836 (Print) 2218-5836 (Linking). doi: 10.5312/wjo.v6.i1.24.
3. Kemal Nas, Levent Yazmalar, Volkan Şah, Abdulkadir Aydın, and Kadriye Öneş. Rehabilitation of spinal cord injuries. *World Journal of Orthopedics*, 6(1):8–16, 2015. ISSN 2218-5836. doi: 10.5312/wjo.v6.i1.8.
4. Christine Migliorini, Bruce Tonge, and George Taleporos. Spinal cord injury and mental health. *Australian & New Zealand Journal of Psychiatry*, 42(4):309–314, 2008. ISSN 0004-8674. doi: 10.1080/00048670801886080.
5. Kim D. Anderson. Targeting recovery: Priorities of the spinal cord-injured population. *Journal of Neurotrauma*, 21(10):1371–1383, 2004. doi: 10.1089/neu.2004.21.1371.
6. M Diop, D Epstein, and A Gaggero. Quality of life, health and social costs of patients with spinal cord injury: A systematic review. *European Journal of Public Health*, 31 (Supplement_3):ckab165.177, October 2021. ISSN 1101-1262. doi: 10.1093/eurpub/ckab165.177.
7. Public Health Agency of Canada. Chronic Diseases and Injuries in Canada. https://www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-33-no-3-2013/economic-burden-traumatic-spinal-cord-injury-canada.html, May 2013.
8. David McDaid, A-La Park, Angela Gall, Mariel Purcell, and Mark Bacon. Understanding and modelling the economic impact of spinal cord injuries in the United Kingdom. *Spinal Cord*, 57(9):778–788, September 2019. ISSN 1476-5624. doi: 10.1038/s41393-019-0285-1.
9. M. J. DeVivo. Causes and costs of spinal cord injury in the United States. *Spinal Cord*, 35 (12):809–813, December 1997. ISSN 1362-4393. doi: 10.1038/sj.sc.3100501.
10. AlphaBeta Australia. Spinal Cord Injury in Australia Commissioned by Spinal Cure Australia and Insurance and Care NSW (iCare). Technical report, Accenture, Sydney, Australia, 2020.
11. Shivayogi V. Hiremath, Nathan S. Hogaboom, Melissa R. Roscher, Lynn A. Worobey, Michelle L. Oyster, and Michael L. Boninger. Longitudinal Prediction of Quality-of-Life Scores and Locomotion in Individuals With Traumatic Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation*, 98(12):2385–2392, December 2017. ISSN 0003-9993. doi: 10.1016/j.apmr.2017.05.020.
12. John Ditunno and Giorgio Scivoletto. Clinical relevance of gait research applied to clinical trials in spinal cord injury. *Brain Research Bulletin*, 78(1):35–42, January 2009. ISSN 0361-9230. doi: 10.1016/j.brainresbull.2008.09.003.
13. K. Akazawa, J. W. Aldridge, J. D. Steeves, and R. B. Stein. Modulation of stretch reflexes during locomotion in the mesencephalic cat. *The Journal of Physiology*, 329(1):553–567, 1982. ISSN 0022-3751. doi: 10.1113/jphysiol.1982.sp014319.
14. H. Zhong, R. R. Roy, K. K. Nakada, S. Zdunowski, N. Khalili, R. D. de Leon, and V. R. Edgerton. Accommodation of the spinal cat to a tripping perturbation. *Frontiers in physiology*, 3:112, 2012. ISSN 1664-042X (Electronic) 1664-042X (Linking). doi: 10.3389/fphys.2012.00112.
15. E. D. Schomburg, N. Petersen, I. Barajon, and H. Hultborn. Flexor reflex afferents reset the step cycle during fictive locomotion in the cat. *Experimental Brain Research*, 122(3): 339–350, October 1998. ISSN 0014-4819. doi: 10.1007/s002210050522.
16. James W. Little, Paula Micklesen, Robert Umlauf, and Catherine Britell. Lower Extremity Manifestations of Spasticity in Chronic Spinal Cord Injury. *American Journal of Physical Medicine & Rehabilitation*, 68(1):32, February 1989. ISSN 0894-9115.
17. Brian D. Schmit, Alicia McKenna-Cole, and W. Zev Rymer. Flexor reflexes in chronic spinal cord injury triggered by imposed ankle rotation. *Muscle & Nerve*, 23(5):793–803, 2000. ISSN 1097-4598. doi: 10.1002/(SICI)1097-4598(200005)23:5<793::AID-MUS18>3.0.CO;2-T.
18. J. Harnie, A. Doelman, E. de Vette, J. Audet, E. Desrochers, N. Gaudreault, and A. Frigon. The recovery of standing and locomotion after spinal cord injury does not require task-specific training. *Elife*, 8, 2019. ISSN 2050-084X (Electronic) 2050-084X (Linking). doi: 10.7554/eLife.50134.
19. Janine Beauparlant, Rubia Van Den Brand, Quentin Barraud, Lucia Friedli, Pavel Musienko, Volker Dietz, and Grégoire Courtine. Undirected compensatory plasticity contributes to neuronal dysfunction after severe spinal cord injury. *Brain : a journal of neurology*, 136(11):3347–3361, 2013. ISSN 1460-2156. doi: 10.1093/brain/awt204.
20. James V. Lynskey, Adam Belanger, and Ranu Jung. Activity-dependent plasticity in spinal cord injury. *Journal of rehabilitation research and development*, 45(2):229–240, 2008. ISSN 0748-7711. doi: 10.1682/JRRD.2007.03.0047.
21. V. R. Edgerton, N. J. Tillakaratne, A. J. Bigbee, R. D. de Leon, and R. R. Roy. Plasticity of the spinal neural circuitry after injury. *Annual review of neuroscience*, 27:145–67, 2004. ISSN 0147-006X (Print) 0147-006X (Linking). doi: 10.1146/annurev.neuro.27.070203.144308.
22. Carmelo Bellardita, Vittorio Caggiano, Roberto Leiras, Vanessa Caldeira, Andrea Fuchs, Julien Bouvier, Peter Löw, and Ole Kiehn. Spatiotemporal correlation of spinal network dynamics underlying spasms in chronic spinalized mice. *eLife*, 6, 2017. ISSN 2050-084X. doi: 10.7554/elife.23011.
23. M. M. Dimitrijevic, M. R. Dimitrijevic, L. S. Illis, K. Nakajima, P. C. Sharkey, and A. M. Sherwood. Spinal cord stimulation for the control of spasticity in patients with chronic spinal cord injury: I. Clinical observations. *Central nervous system trauma : journal of the American Paralysis Association*, 3(2):129–44, 1986. ISSN 0737-5999 (Print) 0737-5999. doi: 10.1089/cns.1986.3.129.
24. Mm Pinter, F. Gerstenbrand, and Mr Dimitrijevic. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 3. Control of spasticity. *Spinal cord : the official journal of the International Medical Society of Paraplegia*, 38(9):524–531, 2000. ISSN 1362-4393. doi: 10.1038/sj.sc.3101040.
25. K. C. Cowley and B. J. Schmidt. Effects of inhibitory amino acid antagonists on reciprocal inhibitory interactions during rhythmic motor activity in the in vitro neonatal rat spinal cord. *Journal of Neurophysiology*, 74(3):1109–1117, 1995. ISSN 0022-3077. doi: 10.1152/jn.1995.74.3.1109.
26. W. B. McKay, A. V. Ovechkin, T. W. Vitaz, D. G. L. Terson de Paleville, and S. J. Harkema. Long-lasting involuntary motor activity after spinal cord injury. *Spinal Cord*, 49(1):87–93, January 2011. ISSN 1476-5624. doi: 10.1038/sc.2010.73.
27. Susan Harkema, Yury Gerasimenko, Jonathan Hodes, Joel Burdick, Claudia Angeli, Yangsheng Chen, Christie Ferreira, Andrea Willhite, Enrico Rejc, Robert G. Grossman, and V. Reggie Edgerton. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: A case study. *The Lancet*, 377(9781):1938–1947, 2011. ISSN 01406736. doi: 10.1016/s0140-6736(11)60547-3.
28. Parag Gad, Yury Gerasimenko, Sharon Zdunowski, Amanda Turner, Dimitry Sayenko, Daniel C. Lu, and V. Reggie Edgerton. Weight bearing over-ground stepping in an exoskeleton with non-invasive spinal cord neuromodulation after motor complete paraplegia. *Frontiers in Neuroscience*, 11, 2017. ISSN 1662-453X. doi: 10.3389/fnins.2017.00333.
29. E. Rejc, C. A. Angeli, D. Atkinson, and S. J. Harkema. Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. *Scientific reports*, 7(1):13476, 2017. ISSN 2045-2322 (Electronic) 2045-2322 (Linking). doi: 10.1038/s41598-017-14003-w.
30. Andreas Rowald, Salif Komi, Robin Demesmaeker, Edeny Baaklini, Sergio Daniel Hernandez-Charpak, Edoardo Paoles, Hazael Montanaro, Antonino Cassara, Fabio Becce, Bryn Lloyd, Taylor Newton, Jimmy Ravier, Nawal Kinany, Marina D'Ercole, Aurélie Paley, Nicolas Hankov, Camille Varescon, Laura McCracken, Molywan Vat, Miroslav Caban, Anne Watrin, Charlotte Jacquet, Léa Bole-Feysot, Cathal Harte, Henri Lorach, Andrea Galvez, Manon Tschopp, Natacha Herrmann, Moïra Wacker, Lionel Geernaert, Isabelle Fodor, Valentin Radevich, Katrien Van Den Keybus, Grégoire Eberle, Etienne Pralong, Maxime Roulet, Jean-Baptiste Ledoux, Eleonora Fornari, Stefano Mandija, Loan Mattera, Roberto Martuzzi, Bruno Nazarian, Stefan Benkler, Simone Callegari, Nathan Greiner, Benjamin Fuhrer, Martijn Froeling, Nik Buse, Tim Denison, Rik Buschman, Christian Wende, Damien Ganty, Jurriaan Bakker, Vincent Delattre, Hendrik Lambert, Karen Minassian, Cornelis A. T. van den Berg, Anne Kavounoudias, Silvestro Micera, Dimitri Van De Ville, Quentin Barraud, Erkan Kurt, Niels Kuster, Esra Neufeld, Marco Capogrosso, Leonie Asboth, Fabien B. Wagner, Jocelyne Bloch, and Grégoire Courtine. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. *Nature Medicine*, 28(2):260–271, February 2022. ISSN 1546-170X. doi: 10.1038/s41591-021-01663-5.
31. Henri Lorach, Andrea Galvez, Valeria Spagnolo, Felix Martel, Serpil Karakas, Nadine Intering, Molywan Vat, Olivier Faivre, Cathal Harte, Salif Komi, Jimmy Ravier, Thibault Collin, Laure Coquoz, Icare Sakr, Edeny Baaklini, Sergio Daniel Hernandez-Charpak, Gregory Dumont, Rik Buschman, Nicholas Buse, Tim Denison, Ilse van Nes, Leonie Asboth, Anne Watrin, Lucas Struber, Fabien Sauter-Starace, Lilia Langar, Vincent Auboiroux, Stefano Carda, Stephan Chabardes, Tetiana Aksenova, Robin Demesmaeker, Guillaume Charvet, Jocelyne Bloch, and Grégoire Courtine. Walking naturally after spinal cord injury using a brain-spine interface. *Nature*, 618(7963):126–133, June 2023. ISSN 1476-4687. doi: 10.1038/s41586-023-06094-5.
32. Aya Takeoka, Isabel Vollenweider, Grégoire Courtine, and Silvia Arber. Muscle spindle feedback directs locomotor recovery and circuit reorganization after spinal cord injury. *Cell*, 159(7):1626–1639, 2014. ISSN 0092-8674. doi: 10.1016/j.cell.2014.11.019.
33. Aya Takeoka and Silvia Arber. Functional local proprioceptive feedback circuits initiate and maintain locomotor recovery after spinal cord injury. *Cell Reports*, 27(1):71–85.e3, 2019. ISSN 2211-1247. doi: 10.1016/j.celrep.2019.03.010.
34. Turgay Akay, Warren G. Tourtellotte, Silvia Arber, and Thomas M. Jessell. Degradation of mouse locomotor pattern in the absence of proprioceptive sensory feedback. *Proceedings of the National Academy of Sciences*, 111(47):16877–16882, 2014. ISSN 0027-8424. doi: 10.1073/pnas.1419045111.
35. I. Lavrov, Y. P. Gerasimenko, R. M. Ichiyama, G. Courtine, H. Zhong, R. R. Roy, and V. R. Edgerton. Plasticity of spinal cord reflexes after a complete transection in adult rats: Relationship to stepping ability. *Journal of neurophysiology*, 96(4):1699–710, 2006. ISSN 0022-3077 (Print) 0022-3077 (Linking). doi: 10.1152/jn.00325.2006.
36. Jamie R. Flynn, Brett A. Graham, Mary P. Galea, and Robert J. Callister. The role of propriospinal interneurons in recovery from spinal cord injury. *Neuropharmacology*, 60(5): 809–822, 2011. ISSN 0028-3908. doi: 10.1016/j.neuropharm.2011.01.016.
37. M. P. Cote, L. M. Murray, and M. Knikou. Spinal control of locomotion: Individual neurons, their circuits and functions. *Frontiers in physiology*, 9:784, 2018. ISSN 1664-042X (Print) 1664-042X (Linking). doi: 10.3389/fphys.2018.00784.
38. Niranjala J. K. Tillakaratne, Paul Duru, Hidemi Fujino, Hui Zhong, Mei Si Xiao, V. Reggie Edgerton, and Roland R. Roy. Identification of interneurons activated at different inclines during treadmill locomotion in adult rats. *Journal of Neuroscience Research*, 92(12):1714–1722, 2014. ISSN 0360-4012. doi: 10.1002/jnr.23437.
39. Peng Liu, Xiao Zhang, Xiaolan He, Zhenhua Jiang, Qun Wang, and Yan Lu. Spinal GABAergic neurons are under feed-forward inhibitory control driven by Aδ and C fibers in Gad2 td-Tomato mice. *Molecular Pain*, 17:1744806921992620, January 2021. ISSN 1744-8069. doi: 10.1177/1744806921992620.
40. Yuka Nakamura, Miyuki Kurabe, Mami Matsumoto, Tokiharu Sato, Satoshi Miyashita, Kana Hoshina, Yoshinori Kamiya, Kazuki Tainaka, Hitoshi Matsuzawa, Nobuhiko Ohno, and Masaki Ueno. Cerebrospinal fluid-contacting neuron tracing reveals structural and functional connectivity for locomotion in the mouse spinal cord. *eLife*, 12:e83108, February 2023. ISSN 2050-084X. doi: 10.7554/eLife.83108.
41. Laskaro Zagoraiou, Turgay Akay, James F. Martin, Robert M. Brownstone, Thomas M. Jessell, and Gareth B. Miles. A cluster of cholinergic premotor interneurons modulates mouse locomotor activity. *Neuron*, 64(5):645–662, 2009. ISSN 1097-4199 0896-6273. doi: 10.1016/j.neuron.2009.10.017.

42. Daniel C. Lu, Tianyi Niu, and William A. Alaynick. Molecular and cellular development of spinal cord locomotor circuitry. *Frontiers in Molecular Neuroscience*, 8(25), 2015. ISSN 1662-5099. doi: 10.3389/fnmol.2015.00025.
43. Filipe Nascimento, Matthew James Broadhead, Efstathia Tetringa, Eirini Tsape, Laskaro Zagoraiou, and Gareth Brian Miles. Synaptic mechanisms underlying modulation of locomotor-related motoneuron output by premotor cholinergic interneurons. *eLife*, 9, 2020. ISSN 2050-084X. doi: 10.7554/elife.54170.
44. Jingwen Niu, Long Ding, Jian J. Li, Hyukmin Kim, Jiakun Liu, Haipeng Li, Andrew Moberly, Tudor C. Badea, Ian D. Duncan, Young-Jin Son, Steven S. Scherer, and Wenqin Luo. Modality-based organization of ascending somatosensory axons in the direct dorsal column pathway. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 33(45):17691–17709, 2013. ISSN 1529-2401 0270-6474. doi: 10.1523/JNEUROSCI.3429-13.2013.
45. Robert M. Brownstone, Tuan V. Bui, and Nicolas Stifani. Spinal circuits for motor learning. *Current Opinion in Neurobiology*, 33:166–173, 2015. ISSN 0959-4388. doi: 10.1016/j.conb.2015.04.007.
46. Alex M. Laliberte, Sara Goltash, Nicolas R. Lalonde, and Tuan Vu Bui. Propriospinal neurons: Essential elements of locomotor control in the intact and possibly the injured spinal cord. *Frontiers in Cellular Neuroscience*, 13, 2019. ISSN 1662-5102. doi: 10.3389/fncel.2019.00512.
47. Jamie Flynn, Victoria Conn, Kieran Boyle, David Hughes, Masahiko Watanabe, Tomoko Velasquez, Martyn Goulding, Robert Callister, and Brett Graham. Anatomical and molecular properties of long descending propriospinal neurons in mice. *Frontiers in Neuroanatomy*, 11(5), 2017. ISSN 1662-5129. doi: 10.3389/fnana.2017.00005.
48. J. T. Eisdorfer, R. D. Smit, K. M. Keefe, M. A. Lemay, G. M. Smith, and A. J. Spence. Epidural electrical stimulation: A review of plasticity mechanisms that are hypothesized to underlie enhanced recovery from spinal cord injury with stimulation. *Frontiers in molecular neuroscience*, 13:163, 2020. ISSN 1662-5099 (Print) 1662-5099 (Linking). doi: 10.3389/fnmol.2020.00163.
49. L. Filli, A. K. Engmann, B. Zorner, O. Weinmann, T. Moraitis, M. Gullo, H. Kasper, R. Schneider, and M. E. Schwab. Bridging the gap: A reticulo-propriospinal detour bypassing an incomplete spinal cord injury. *Journal of Neuroscience*, 34(40):13399–13410, 2014. ISSN 0270-6474. doi: 10.1523/jneurosci.0701-14.2014.
50. G. Taccola, D. Sayenko, P. Gad, Y. Gerasimenko, and V. R. Edgerton. And yet it moves: Recovery of volitional control after spinal cord injury. *Progress in neurobiology*, 160:64–81, 2018. ISSN 1873-5118 (Electronic) 0301-0082 (Linking). doi: 10.1016/j.pneurobio.2017.10.004.
51. Y. Gerasimenko, P. Musienko, I. Bogacheva, T. Moshonkina, A. Savochin, I. Lavrov, R. R. Roy, and V. R. Edgerton. Propriospinal bypass of the serotonergic system that can facilitate stepping. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29(17):5681–9, 2009. ISSN 1529-2401 (Electronic) 0270-6474 (Linking). doi: 10.1523/JNEUROSCI.6058-08.2009.
52. G. Courtine, B. Song, R. R. Roy, H. Zhong, J. E. Herrmann, Y. Ao, J. Qi, V. R. Edgerton, and M. V. Sofroniew. Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. *Nature medicine*, 14(1):69–74, 2008. ISSN 1546-170X (Electronic) 1078-8956 (Linking). doi: 10.1038/nm1682.
53. C. Truchon, N. Fallah, A. Santos, J. Vachon, V. K. Noonan, and C. L. Cheng. Impact of therapy on recovery during rehabilitation in patients with traumatic spinal cord injury. *Journal of neurotrauma*, 34(20):2901–2909, 2017. ISSN 1557-9042 (Electronic) 0897-7151 (Linking). doi: 10.1089/neu.2016.4932.
54. M. Capogrosso, T. Milekovic, D. Borton, F. Wagner, E. M. Moraud, J. B. Mignardot, N. Buse, J. Gandar, Q. Barraud, D. Xing, E. Rey, S. Duis, Y. Jianzhong, W. K. Ko, Q. Li, P. Detemple, T. Denison, S. Micera, E. Bezard, J. Bloch, and G. Courtine. A brain-spine interface alleviating gait deficits after spinal cord injury in primates. *Nature*, 539(7628):284–288, 2016. ISSN 1476-4687 (Electronic) 0028-0836 (Linking). doi: 10.1038/nature20118.
55. Parag Gad, Jaehoon Choe, Prithvi Shah, Guillermo Garcia-Alias, Mrinal Rath, Yury Gerasimenko, Hui Zhong, Roland R. Roy, and Victor Reggie Edgerton. Sub-threshold spinal cord stimulation facilitates spontaneous motor activity in spinal rats. *Journal of NeuroEngineering and Rehabilitation*, 10:108–108, 2013. ISSN 1743-0003. doi: 10.1186/1743-0003-10-108.
56. G. Courtine, Y. Gerasimenko, R. van den Brand, A. Yew, P. Musienko, H. Zhong, B. Song, Y. Ao, R. M. Ichiyama, I. Lavrov, R. R. Roy, M. V. Sofroniew, and V. R. Edgerton. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nature neuroscience*, 12(10):1333–42, 2009. ISSN 1546-1726 (Electronic) 1097-6256 (Linking). doi: 10.1038/nn.2401.
57. P. Gad, I. Lavrov, P. Shah, H. Zhong, R. R. Roy, V. R. Edgerton, and Y. Gerasimenko. Neuromodulation of motor-evoked potentials during stepping in spinal rats. *Journal of neurophysiology*, 110(6):1311–22, 2013. ISSN 1522-1598 (Electronic) 0022-3077 (Linking). doi: 10.1152/jn.00169.2013.
58. Y. Gerasimenko, R. Gorodnichev, A. Puhov, T. Moshonkina, A. Savochin, V. Selionov, R. R. Roy, D. C. Lu, and V. R. Edgerton. Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. *Journal of neurophysiology*, 113(3):834–42, 2015. ISSN 1522-1598 (Electronic) 0022-3077 (Linking). doi: 10.1152/jn.00609.2014.
59. E. M. Moraud, M. Capogrosso, E. Formento, N. Wenger, J. DiGiovanna, G. Courtine, and S. Micera. Mechanisms underlying the neuromodulation of spinal circuits for correcting gait and balance deficits after spinal cord injury. *Neuron*, 89(4):814–28, 2016. ISSN 1097-4199 (Electronic) 0896-6273 (Linking). doi: 10.1016/j.neuron.2016.01.009.
60. V. R. Edgerton, G. Courtine, Y. P. Gerasimenko, I. Lavrov, R. M. Ichiyama, A. J. Fong, L. L. Cai, C. K. Otoshi, N. J. Tillakaratne, J. W. Burdick, and R. R. Roy. Training locomotor networks. *Brain research reviews*, 57(1):241–54, 2008. ISSN 0165-0173 (Print) 0165-0173 (Linking). doi: 10.1016/j.brainresrev.2007.09.002.
61. M. Capogrosso, N. Wenger, S. Raspopovic, P. Musienko, J. Beauparlant, L. Bassi Luciani, G. Courtine, and S. Micera. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 33(49):19326–40, 2013. ISSN 1529-2401 (Electronic) 0270-6474 (Linking). doi: 10.1523/JNEUROSCI.1688-13.2013.
62. Emanuele Formento, Karen Minassian, Fabien Wagner, Jean Baptiste Mignardot, Camille G. Le Goff-Mignardot, Andreas Rowald, Jocelyne Bloch, Silvestro Micera, Marco Capogrosso, and Gregoire Courtine. Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal cord injury. *Nature Neuroscience*, 21(12):1728–1741, 2018. ISSN 1546-1726. doi: 10.1038/s41593-018-0262-6.
63. C. A. Angeli, V. R. Edgerton, Y. P. Gerasimenko, and S. J. Harkema. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain : a journal of neurology*, 137(Pt 5):1394–409, 2014. ISSN 1460-2156 (Electronic) 0006-8950 (Linking). doi: 10.1093/brain/awu038.
64. Simon M. Danner, Ursula S. Hofstoetter, Brigitta Freundl, Heinrich Binder, Winfried Mayr, Frank Rattay, and Karen Minassian. Human spinal locomotor control is based on flexibly organized burst generators. *Brain : a journal of neurology*, 138(3):577–588, 2015. ISSN 1460-2156. doi: 10.1093/brain/awu372.
65. Jacob Caylor, Rajiv Reddy, Sopyda Yin, Christina Cui, Mingxiong Huang, Charles Huang, Ramesh Rao, Dewleen G. Baker, Alan Simmons, Dmitri Souza, Samer Narouze, Ricardo Vallejo, and Imanuel Lerman. Spinal cord stimulation in chronic pain: Evidence and theory for mechanisms of action. *Bioelectronic Medicine*, 5:12, June 2019. ISSN 2332-8886. doi: 10.1186/s42234-019-0023-1.
66. Marcel Stimberg, Romain Brette, and Dan FM Goodman. Brian 2, an intuitive and efficient neural simulator. *eLife*, 8:e47314, August 2019. ISSN 2050-084X. doi: 10.7554/eLife.47314.
67. Hugues Leblond, Marion Espérance, Didier Orsal, and Serge Rossignol. Treadmill locomotion in the intact and spinal mouse. *The Journal of Neuroscience*, 23(36):11411, 2003. doi: 10.1523/JNEUROSCI.23-36-11411.2003.
68. T. V. Bui, S. Cushing, D. Dewey, R. E. Fyffe, and P. K. Rose. Comparison of the morphological and electrotonic properties of Renshaw cells, Ia inhibitory interneurons, and motoneurons in the cat. *Journal of Neurophysiology*, 90(5):2900–2918, November 2003. ISSN 0022-3077. doi: 10.1152/jn.00533.2003.
69. Windyanne Khristy, Noore J. Ali, Arlene B. Bravo, Ray de Leon, Roland R. Roy, Hui Zhong, Nik J. L. London, V. Reggie Edgerton, and Niranjala J. K. Tillakaratne. Changes in GABAA receptor subunit gamma 2 in extensor and flexor motoneurons and astrocytes after spinal cord transection and motor training. *Brain Research*, 1273:9–17, June 2009. ISSN 0006-8993. doi: 10.1016/j.brainres.2009.03.060.
70. Elżbieta Jankowska and W. J. Roberts. Synaptic actions of single interneurones mediating reciprocal Ia inhibition of motoneurones. *The Journal of Physiology*, 222(3):623–642, 1972. ISSN 0022-3751. doi: 10.1113/jphysiol.1972.sp009818.
71. S. A. Edgley and E. Jankowska. An interneuronal relay for group I and II muscle afferents in the midlumbar segments of the cat spinal cord. *The Journal of Physiology*, 389(1): 647–674, 1987. ISSN 0022-3751. doi: 10.1113/jphysiol.1987.sp016676.
72. P. Rudomin. Presynaptic inhibition of muscle spindle and tendon organ afferents in the mammalian spinal cord. *Trends in Neurosciences*, 13(12):499–505, 1990. ISSN 0166-2236. doi: 10.1016/0166-2236(90)90084-N.
73. E. Jankowska. Interneuronal relay in spinal pathways from proprioceptors. *Progress in Neurobiology*, 38(4):335–378, 1992. ISSN 0301-0082. doi: 10.1016/0301-0082(92)90024-9.
74. P. Rudomin and Robert F. Schmidt. Presynaptic inhibition in the vertebrate spinal cord revisited. *Experimental Brain Research*, 129(1):1–37, 1999. ISSN 0014-4819. doi: 10.1007/s002210050933.
75. G. Zhong, S. Droho, S. A. Crone, S. Dietz, A. C. Kwan, W. W. Webb, K. Sharma, and R. M. Harris-Warrick. Electrophysiological characterization of V2a interneurons and their locomotor-related activity in the neonatal mouse spinal cord. *Journal of Neuroscience*, 30(1):170–182, 2010. ISSN 0270-6474. doi: 10.1523/jneurosci.4849-09.2010.
76. Elzbieta Jankowska. Spinal interneurons. In *Neuroscience in the 21st Century: From Basic to Clinical*, pages 1063–1099. Springer New York, 2013. doi: 10.1007/978-1-4614-1997-6_34.
77. K. J. Dougherty and O. Kiehn. Firing and cellular properties of V2a interneurons in the rodent spinal cord. *Journal of Neuroscience*, 30(1):24–37, 2010. ISSN 0270-6474. doi: 10.1523/jneurosci.4821-09.2010.
78. Kimberly J Dougherty, Laskaro Zagoraiou, Daisuke Satoh, Ismini Rozani, Staceyann Doobar, Silvia Arber, Thomas M Jessell, and Ole Kiehn. Locomotor rhythm generation linked to the output of spinal shox2 excitatory interneurons. *Neuron*, 80(4):920–933, 2013. ISSN 0896-6273. doi: 10.1016/j.neuron.2013.08.015.
79. Adolfo, Toshiaki Endo, Peter Löw, Lotta Borgius, Martin Hägglund, Kimberly, Jesper Ryge, Thomas, and Ole Kiehn. Identification of minimal neuronal networks involved in flexor-extensor alternation in the mammalian spinal cord. *Neuron*, 71(6):1071–1084, 2011. ISSN 0896-6273. doi: 10.1016/j.neuron.2011.07.011.
80. Andrew J. P. Fink, Katherine R. Croce, Z. Josh Huang, L. F. Abbott, Thomas M. Jessell, and Eiman Azim. Presynaptic inhibition of spinal sensory feedback ensures smooth movement. *Nature*, 509(7498):43–48, 2014. ISSN 0028-0836. doi: 10.1038/nature13276.
81. Tuan V. Bui, Nicolas Stifani, Turgay Akay, and Robert M. Brownstone. Spinal microcircuits comprising dI3 interneurons are necessary for motor functional recovery following spinal cord transection. *eLife*, 5, 2016. ISSN 2050-084X. doi: 10.7554/eLife.21715.
82. Stephanie C. Koch, Marta Garcia Del Barrio, Antoine Dalet, Graziana Gatto, Thomas Günther, Jingming Zhang, Barbara Seidler, Dieter Saur, Roland Schüle, and Martyn Goulding. RORβ spinal interneurons gate sensory transmission during locomotion to secure a fluid walking gait. *Neuron*, 96(6):1419–1431.e5, 2017. ISSN 0896-6273. doi: 10.1016/j.neuron.2017.11.011.
83. David B. MacDonald. Intraoperative motor evoked potential monitoring: Overview and update. *Journal of Clinical Monitoring and Computing*, 20(5):347–377, 2006. ISSN 1573-2614. doi: 10.1007/s10877-006-9033-0.
84. Richard Naud, Nicolas Marcille, Claudia Clopath, and Wulfram Gerstner. Firing patterns in the adaptive exponential integrate-and-fire model. *Biological Cybernetics*, 99(4):335–347, November 2008. ISSN 1432-0770. doi: 10.1007/s00422-008-0264-7.
85. Andreas Husch, Shelby B. Dietz, Diana N. Hong, and Ronald M. Harris-Warrick. Adult spinal V2a interneurons show increased excitability and serotonin-dependent bistability.

Journal of Neurophysiology, 113(4):1124–1134, 2014. ISSN 0022-3077. doi: 10.1152/jn.00741.2014.

86. Mathias Kristiansen, Nikolaj Odderskær, and Daniel Haaning Kristensen. Effect of body weight support on muscle activation during walking on a lower body positive pressure treadmill. *Journal of Electromyography and Kinesiology*, 48:9–16, October 2019. ISSN 1050-6411. doi: 10.1016/j.jelekin.2019.05.021.
87. Arthur Prochazka. Chapter 11 quantifying proprioception. In M. D. Binder, editor, *Progress in Brain Research*, volume 123, pages 133–142. Elsevier, 1999. ISBN 0079-6123. doi: 10.1016/S0079-6123(08)62850-2.
88. Kristine C. Cowley, Eugene Zaporozhets, and Brian J. Schmidt. Propriospinal transmission of the locomotor command signal in the neonatal rat. *Annals of the New York Academy of Sciences*, 1198(1):42–53, 2010. ISSN 0077-8923. doi: 10.1111/j.1749-6632.2009.05421.x.
89. Myungin Baek, Chiara Pivetta, Jeh-Ping Liu, Silvia Arber, and Jeremy S. Dasen. Columnar-intrinsic cues shape premotor input specificity in locomotor circuits. *Cell Reports*, 21(4):867–877, 2017. ISSN 2211-1247. doi: 10.1016/j.celrep.2017.10.004.
90. Loubna Khalki, Karina Sadlaoud, Julie Lerond, Jacques-Olivier Coq, Jean-Michel Brezun, Laurent Vinay, Patrice Coulon, and Hélène Bras. Changes in innervation of lumbar motoneurons and organization of premotor network following training of transected adult rats. *Experimental Neurology*, 299:1–14, January 2018. ISSN 0014-4886. doi: 10.1016/j.expneurol.2017.09.002.
91. Marito Hayashi, Christopher A. Hinckley, Shawn P. Driscoll, Niall J. Moore, Ariel J. Levine, Kathryn L. Hilde, Kamal Sharma, and Samuel L. Pfaff. Graded Arrays of Spinal and Supraspinal V2a Interneuron Subtypes Underlie Forelimb and Hindlimb Motor Control. *Neuron*, 97(4):869, February 2018. doi: 10.1016/j.neuron.2018.01.023.
92. Tuan, Turgay Akay, Osama Loubani, Thomas, Thomas, and Robert. Circuits for grasping: Spinal dI3 interneurons mediate cutaneous control of motor behavior. *Neuron*, 78(1):191–204, 2013. ISSN 0896-6273. doi: 10.1016/j.neuron.2013.02.007.
93. Wen-Yuan Li, Ling-Xiao Deng, Feng-Guo Zhai, Xiao-Yu Wang, Zhi-Gang Li, and Ying Wang. Chx10+V2a interneurons in spinal motor regulation and spinal cord injury. *Neural Regeneration Research*, 18(5):933–939, October 2022. ISSN 1673-5374. doi: 10.4103/1673-5374.355746.
94. Mustafa Görkem Özyurt, Julia Ojeda-Alonso, Marco Beato, and Filipe Nascimento. In vitro longitudinal lumbar spinal cord preparations to study sensory and recurrent motor microcircuits of juvenile mice. *Journal of Neurophysiology*, 128(3):711–726, September 2022. ISSN 1522-1598. doi: 10.1152/jn.00184.2022.
95. Arnault H. Caillet, Andrew T. M. Phillips, Dario Farina, and Luca Modenese. Estimation of the firing behaviour of a complete motoneuron pool by combining electromyography signal decomposition and realistic motoneuron modelling. *PLOS Computational Biology*, 18(9): e1010556, September 2022. ISSN 1553-7358. doi: 10.1371/journal.pcbi.1010556.
96. V. Booth, J. Rinzel, and O. Kiehn. Compartmental model of vertebrate motoneurons for Ca2+-dependent spiking and plateau potentials under pharmacological treatment. *Journal of Neurophysiology*, 78(6):3371–3385, December 1997. ISSN 0022-3077. doi: 10.1152/jn.1997.78.6.3371.
97. J. B. Munson, J. W. Fleshman, and G. W. Sypert. Properties of single-fiber spindle group II EPSPs in triceps surae motoneurons. *Journal of Neurophysiology*, 44(4):713–725, October 1980. ISSN 0022-3077. doi: 10.1152/jn.1980.44.4.713.
98. I. Segev, Jr. Fleshman, J. W., and R. E. Burke. Computer simulation of group Ia EPSPs using morphologically realistic models of cat alpha-motoneurons. *Journal of neurophysiology*, 64(2):648–60, 1990. ISSN 0022-3077 (Print) 0022-3077. doi: 10.1152/jn.1990.64.2.648.
99. Shawn Hochman, Jacob Shreckengost, Hiroshi Kimura, and Jorge Quevedo. Presynaptic inhibition of primary afferents by depolarization: Observations supporting nontraditional mechanisms. *Annals of the New York Academy of Sciences*, 1198(1):140–152, 2010. ISSN 0077-8923. doi: 10.1111/j.1749-6632.2010.05436.x.
100. Nicolas R. Lalonde and Tuan V. Bui. Do spinal circuits still require gating of sensory information by presynaptic inhibition after spinal cord injury? *Current Opinion in Physiology*, 19:113–118, 2021. ISSN 2468-8673. doi: 10.1016/j.cophys.2020.10.001.
101. Laura Bella Naumann and Henning Sprekeler. Presynaptic inhibition rapidly stabilises recurrent excitation in the face of plasticity. *PLOS Computational Biology*, 16(8):e1008118, 2020. ISSN 1553-7358. doi: 10.1371/journal.pcbi.1008118.
102. Scott J. Day and Manuel Hulliger. Experimental Simulation of Cat Electromyogram: Evidence for Algebraic Summation of Motor-Unit Action-Potential Trains. *Journal of Neurophysiology*, 86(5):2144–2158, November 2001. ISSN 0022-3077. doi: 10.1152/jn.2001.86.5.2144.
103. Y. P. Gerasimenko, I. A. Lavrov, G. Courtine, R. M. Ichiyama, C. J. Dy, H. Zhong, R. R. Roy, and V. R. Edgerton. Spinal cord reflexes induced by epidural spinal cord stimulation in normal awake rats. *Journal of neuroscience methods*, 157(2):253–63, 2006. ISSN 0165-0270 (Print) 0165-0270 (Linking). doi: 10.1016/j.jneumeth.2006.05.004.
104. R. R. Roy, D. L. Hutchison, D. J. Pierotti, J. A. Hodgson, and V. R. Edgerton. EMG patterns of rat ankle extensors and flexors during treadmill locomotion and swimming. *Journal of applied physiology (Bethesda, Md. : 1985)*, 70(6):2522–9, 1991. ISSN 8750-7587 (Print) 0161-7567. doi: 10.1152/jappl.1991.70.6.2522.
105. Monica Gorassini, Torsten Eken, David J. Bennett, Ole Kiehn, and Hans Hultborn. Activity of Hindlimb Motor Units During Locomotion in the Conscious Rat. *Journal of Neurophysiology*, 83(4):2002–2011, April 2000. ISSN 0022-3077. doi: 10.1152/jn.2000.83.4.2002.
106. P. Gad, R. R. Roy, J. Choe, J. Creagmile, H. Zhong, Y. Gerasimenko, and V. R. Edgerton. Electrophysiological biomarkers of neuromodulatory strategies to recover motor function after spinal cord injury. *Journal of neurophysiology*, 113(9):3386–96, 2015. ISSN 1522-1598 (Electronic) 0022-3077 (Linking). doi: 10.1152/jn.00918.2014.
107. J. E. Stewart, H. Barbeau, and S. Gauthier. Modulation of locomotor patterns and spasticity with clonidine in spinal cord injured patients. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*, 18(3):321–332, 1991. ISSN 0317-1671. doi: 10.1017/s0317167100031887.
108. V. Reggie Edgerton and Roland R. Roy. Spasticity: A switch from inhibition to excitation. *Nature Medicine*, 16(3):270–271, 2010. ISSN 1078-8956. doi: 10.1038/nm0310-270.
109. Yun Guan, Kerry Bradley, John L. Parker, Elliot S. Krames, and Bengt Linderoth. Chapter 15 - spinal cord stimulation: Mechanisms of action. In Elliot S. Krames, P. Hunter Peckham, and Ali R. Rezai, editors, *Neuromodulation (Second Edition)*, pages 161–178. Academic Press, 2018. ISBN 978-0-12-805353-9. doi: 10.1016/B978-0-12-805353-9.00015-2.
110. Koen P.V. Meuwissen, Luuk E. de Vries, Jianwen Wendy Gu, Tianhe C. Zhang, and Elbert A.J. Joosten. Burst and Tonic Spinal Cord Stimulation Both Activate Spinal GABAergic Mechanisms to Attenuate Pain in a Rat Model of Chronic Neuropathic Pain. *Pain Practice*, 20(1):75–87, 2020. ISSN 1533-2500. doi: 10.1111/papr.12831.
111. N. Wenger, E. M. Moraud, J. Gandar, P. Musienko, M. Capogrosso, L. Baud, C. G. Le Goff, Q. Barraud, N. Pavlova, N. Dominici, I. R. Minev, L. Asboth, A. Hirsch, S. Duis, J. Kreider, A. Mortera, O. Haverbeck, S. Kraus, F. Schmitz, J. DiGiovanna, R. van den Brand, J. Bloch, P. Detemple, S. P. Lacour, E. Bezard, S. Micera, and G. Courtine. Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. *Nature medicine*, 22(2):138–45, 2016. ISSN 1546-170X (Electronic) 1078-8956 (Linking). doi: 10.1038/nm.4025.
112. Anas R. Alashram, Elvira Padua, Manikandan Raju, Cristian Romagnoli, and Giuseppe Annino. Transcutaneous spinal cord stimulation effects on spasticity in patients with spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine*, 46(4):582–589, 2023. ISSN 1079-0268. doi: 10.1080/10790268.2021.2000200.
113. Amr Mahrous, Derin Birch, C. J. Heckman, and Vicki Tysseling. Muscle Spasms after Spinal Cord Injury Stem from Changes in Motoneuron Excitability and Synaptic Inhibition, Not Synaptic Excitation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 44(1):e1695232023, January 2024. ISSN 1529-2401. doi: 10.1523/JNEUROSCI.1695-23.2023.
114. Olivier Alluin, Hugo Delivet-Mongrain, and Serge Rossignol. Inducing hindlimb locomotor recovery in adult rat after complete thoracic spinal cord section using repeated treadmill training with perineal stimulation only. *Journal of Neurophysiology*, 114(3):1931–1946, September 2015. ISSN 0022-3077. doi: 10.1152/jn.00416.2015.
115. Karen Minassian and Ursula S. Hofstoetter. Spinal cord stimulation and augmentative control strategies for leg movement after spinal paralysis in humans. *CNS Neuroscience & Therapeutics*, 22(4):262–270, 2016. ISSN 1755-5930. doi: 10.1111/cns.12530.
116. V. R. Edgerton, R. D. Leon, S. J. Harkema, J. A. Hodgson, N. London, D. J. Reinkensmeyer, R. R. Roy, R. J. Talmadge, N. J. Tillakaratne, W. Timoszyk, and A. Tobin. Retraining the injured spinal cord. *The Journal of physiology*, 533(Pt 1):15–22, 2001. ISSN 0022-3751 1469-7793. doi: 10.1111/j.1469-7793.2001.0015b.x.
117. A. J. Fong, L. L. Cai, C. K. Otoshi, D. J. Reinkensmeyer, J. W. Burdick, R. R. Roy, and V. R. Edgerton. Spinal cord-transected mice learn to step in response to quipazine treatment and robotic training. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 25(50):11738–47, 2005. ISSN 1529-2401 (Electronic) 0270-6474 (Linking). doi: 10.1523/JNEUROSCI.1523-05.2005.
118. L. L. Cai, A. J. Fong, C. K. Otoshi, Y. Liang, J. W. Burdick, R. R. Roy, and V. R. Edgerton. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. *Journal of Neuroscience*, 26(41):10564–10568, 2006. ISSN 0270-6474. doi: 10.1523/jneurosci.2266-06.2006.
119. Akira Sakurai, Arianna N. Tamvacakis, and Paul S. Katz. Recruitment of polysynaptic connections underlies functional recovery of a neural circuit after lesion. *eneuro*, 3(4): ENEURO.0056–16., 2016. ISSN 2373-2822. doi: 10.1523/eneuro.0056-16.2016.
120. Serge Rossignol, Réjean Dubuc, and Jean-Pierre Gossard. Dynamic sensorimotor interactions in locomotion. *Physiological Reviews*, 86(1):89–154, 2006. ISSN 0031-9333. doi: 10.1152/physrev.00028.2005.
121. Audrey L. Hicks and Kathleen A. Martin Ginis. Treadmill training after spinal cord injury: It's not just about the walking. *Journal of Rehabilitation Research and Development*, 45 (2):241–248, 2008. ISSN 1938-1352. doi: 10.1682/jrrd.2007.02.0022.
122. Ki Yeun Nam, Hyun Jung Kim, Bum Sun Kwon, Jin-Woo Park, Ho Jun Lee, and Aeri Yoo. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: A systematic review. *Journal of NeuroEngineering and Rehabilitation*, 14(1):24, March 2017. ISSN 1743-0003. doi: 10.1186/s12984-017-0232-3.
123. Anatol G. Feldman, Mindy F. Levin, Alessandro Garofolini, Daniele Piscitelli, and Lei Zhang. Central pattern generator and human locomotion in the context of referent control of motor actions. *Clinical Neurophysiology*, 132(11):2870–2889, November 2021. ISSN 1388-2457. doi: 10.1016/j.clinph.2021.08.016.
124. Ray D. de Leon, David J. Reinkensmeyer, Wojciech K. Timoszyk, Nicolas J. London, Roland R. Roy, and V. Reggie Edgerton. Chapter 11 Use of robotics in assessing the adaptive capacity of the rat lumbar spinal cord. In L. McKerracher, G. Doucet, and S. Rossignol, editors, *Progress in Brain Research*, volume 137, pages 141–149. Elsevier, 2002. ISBN 0079-6123. doi: 10.1016/S0079-6123(02)37013-4.
125. M. J. Cantoria, P. A. See, H. Singh, and R. D. De Leon. Adaptations in glutamate and glycine content within the lumbar spinal cord are associated with the generation of novel gait patterns in rats following neonatal spinal cord transection. *Journal of Neuroscience*, 31(50):18598–18605, 2011. ISSN 0270-6474. doi: 10.1523/jneurosci.3499-11.2011.
126. C. Pizzolato, M. A. Gunduz, D. Palipana, J. Wu, G. Grant, S. Hall, R. Dennison, R. D. Zafonte, D. G. Lloyd, and Y. D. Teng. Non-invasive approaches to functional recovery after spinal cord injury: Therapeutic targets and multimodal device interventions. *Experimental neurology*, 339:113612, 2021. ISSN 1090-2430 (Electronic) 0014-4886 (Linking). doi: 10.1016/j.expneurol.2021.113612.
127. Anna M. Cabaj, Henryk Majczyński, Erika Couto, Phillip F. Gardiner, Katinka Stecina, Urszula Sławińska, and Larry M. Jordan. Serotonin controls initiation of locomotion and afferent modulation of coordination via 5-HT7receptors in adult rats. *The Journal of Physiology*, 595(1):301–320, 2017. ISSN 0022-3751. doi: 10.1113/jp272271.
128. Y. P. Gerasimenko, R. M. Ichiyama, I. A. Lavrov, G. Courtine, L. Cai, H. Zhong, R. R. Roy, and V. R. Edgerton. Epidural spinal cord stimulation plus quipazine administration enable stepping in complete spinal adult rats. *Journal of neurophysiology*, 98(5):2525–36, 2007. ISSN 0022-3077 (Print) 0022-3077 (Linking). doi: 10.1152/jn.00836.2007.
129. Ronaldo M. Ichiyama, Yury Gerasimenko, Devin L. Jindrich, Hui Zhong, Roland R. Roy, and V. Reggie Edgerton. Dose dependence of the 5-HT agonist quipazine in facilitating spinal stepping in the rat with epidural stimulation. *Neuroscience letters*, 438(3):281–285, 2008. ISSN 0304-3940 1872-7972. doi: 10.1016/j.neulet.2008.04.080.

130. Simon M. Danner, Han Zhang, Natalia A. Shevtsova, Joanna Borowska-Fielding, Dylan Deska-Gauthier, Ilya A. Rybak, and Ying Zhang. Spinal V3 interneurons and Left–Right coordination in mammalian locomotion. *Frontiers in Cellular Neuroscience*, 13(516), 2019. ISSN 1662-5102. doi: 10.3389/fncel.2019.00516.
131. I. A. Rybak, K. J. Dougherty, and N. A. Shevtsova. Organization of the mammalian locomotor CPG: Review of computational model and circuit architectures based on genetically identified spinal Interneurons(1,2,3). *eNeuro*, 2(5), 2015. ISSN 2373-2822 (Print) 2373-2822 (Linking). doi: 10.1523/ENEURO.0069-15.2015.
132. J. Feng. Is the integrate-and-fire model good enough?–a review. *Neural Networks: The Official Journal of the International Neural Network Society*, 14(6-7):955–975, 2001. ISSN 0893-6080. doi: 10.1016/s0893-6080(01)00074-0.
133. Liya Merzon, Tatiana Malevich, Georgiy Zhulikov, Sofia Krasovskaya, and W. Joseph MacInnes. Temporal Limitations of the Standard Leaky Integrate and Fire Model. *Brain Sciences*, 10(1):16, December 2019. ISSN 2076-3425. doi: 10.3390/brainsci10010016.
134. Jeffrey Andrews Edlund. *Numerical Investigation of Spinal Neuron Facilitation with Multi-Electrode Epidural Stimulation*. Thesis, California Institute of Technology, 2019.
135. I. Lavrov, G. Courtine, C. J. Dy, R. van den Brand, A. J. Fong, Y. Gerasimenko, H. Zhong, R. R. Roy, and V. R. Edgerton. Facilitation of stepping with epidural stimulation in spinal rats: Role of sensory input. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 28(31):7774–80, 2008. ISSN 1529-2401 (Electronic) 0270-6474 (Linking). doi: 10.1523/JNEUROSCI.1069-08.2008.
136. I. Lavrov, C. J. Dy, A. J. Fong, Y. Gerasimenko, G. Courtine, H. Zhong, R. R. Roy, and V. R. Edgerton. Epidural stimulation induced modulation of spinal locomotor networks in adult spinal rats. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 28(23):6022–9, 2008. ISSN 1529-2401 (Electronic) 0270-6474 (Linking). doi: 10.1523/JNEUROSCI.0080-08.2008.
137. Zuzanna Brzosko, Susanna B. Mierau, and Ole Paulsen. Neuromodulation of Spike-Timing-Dependent Plasticity: Past, Present, and Future. *Neuron*, 103(4):563–581, August 2019. ISSN 08966273. doi: 10.1016/j.neuron.2019.05.041.
138. Guillaume Caron, Jadwiga N. Bilchak, and Marie-Pascale Côté. Direct evidence for decreased presynaptic inhibition evoked by PBSt group I muscle afferents after chronic SCI and recovery with step-training in rats. *The Journal of Physiology*, 598(20):4621–4642, 2020. ISSN 0022-3751. doi: 10.1113/jp280070.


A
excitatory
inhibitory
presynaptic inhibition
IaIN
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Extensor-Ia
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B
Simulated Afferent Firing Rates
TA Ia
TA II
GM Ia
GM II
Baseline
BWS
Firing Rate (Hz)
Time (% of gait cycle)
C
GABA Synapse Connections
SCI
Baseline
Target neuron index
Source neuron index
Stimulation Connections
Indexes
Stimulation Source
Axon Target
Neural Groups
D
Excitatory Exponential Synapse
Voltage (mV)
Conductivity (nS)
1 nS
3 nS
5 nS
12 nS
15 nS
30 nS
Time (ms)
E
Inhibitory Alpha Synapse
Voltage (mV)
Conductivity (nS)
1 nS
3 nS
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12 nS
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Time (ms)
F
Single Step TA MN Activity
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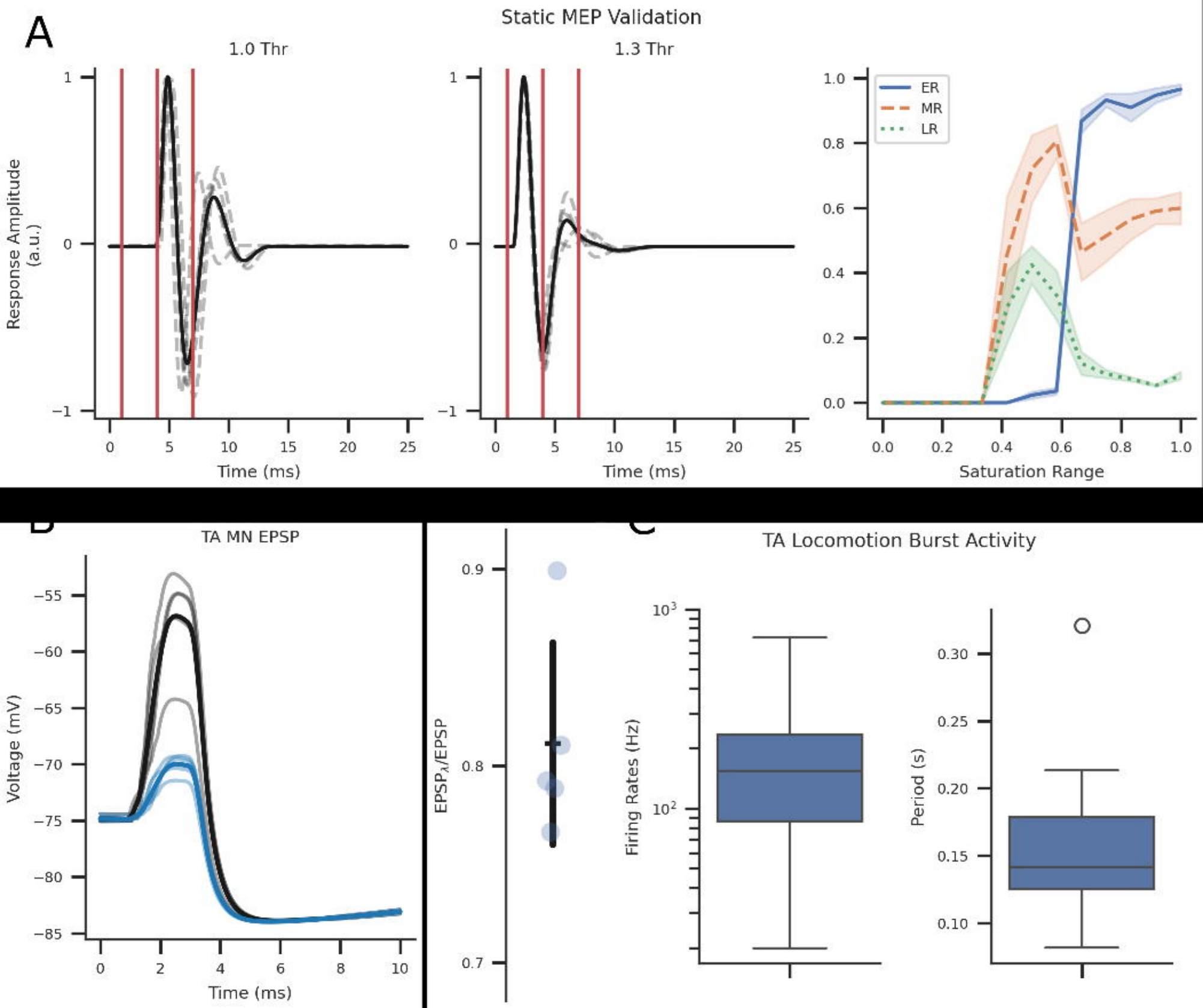
A
Static MEP Validation
1.0 Thr
1.3 Thr
Response Amplitude (a.u.)
Time (ms)
Time (ms)
ER
MR
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Saturation Range
B
TA MN EPSP
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C
TA Locomotion Burst Activity
Firing Rates (Hz)
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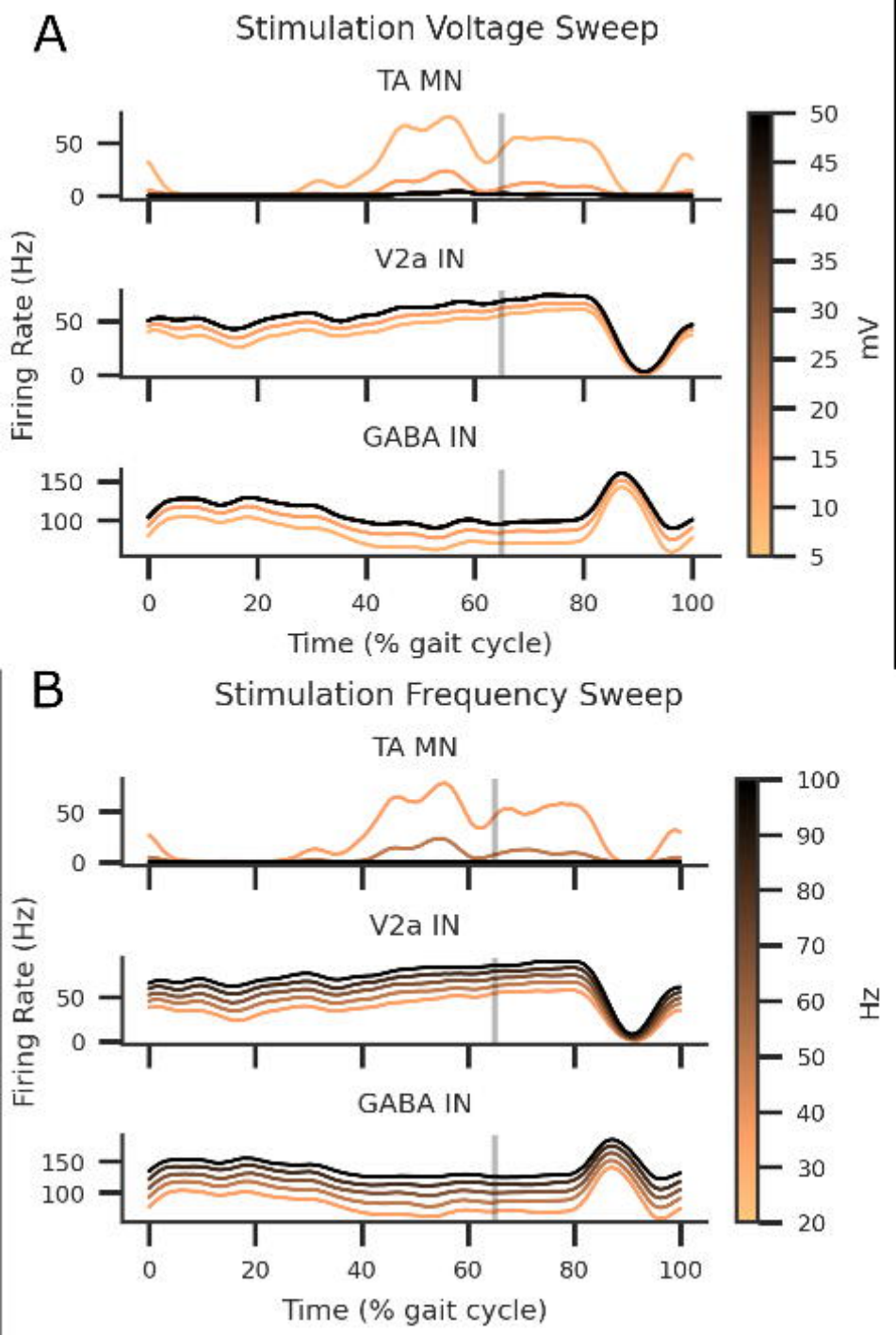
A
Stimulation Voltage Sweep
TA MN
V2a IN
GABA IN
Firing Rate (Hz)
50
0
150
100
0
20
40
60
80
100
Time (% gait cycle)
50
45
40
35
30
25
20
15
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mV
B
Stimulation Frequency Sweep
TA MN
V2a IN
GABA IN
Firing Rate (Hz)
50
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Time (% gait cycle)
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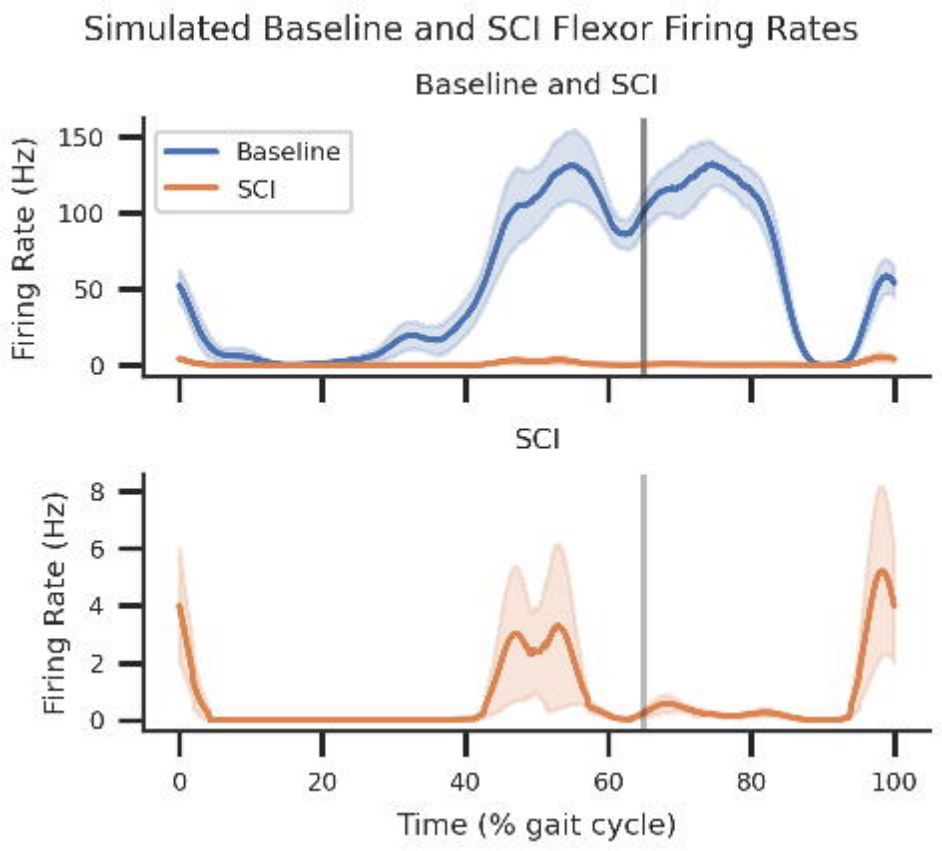
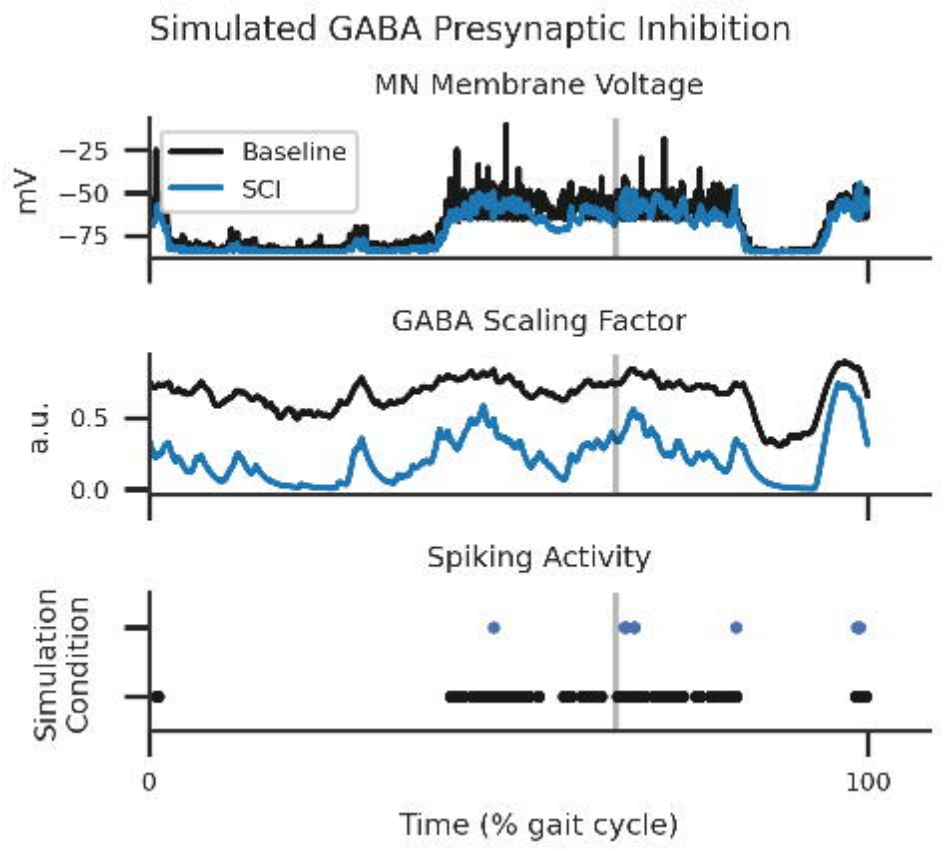
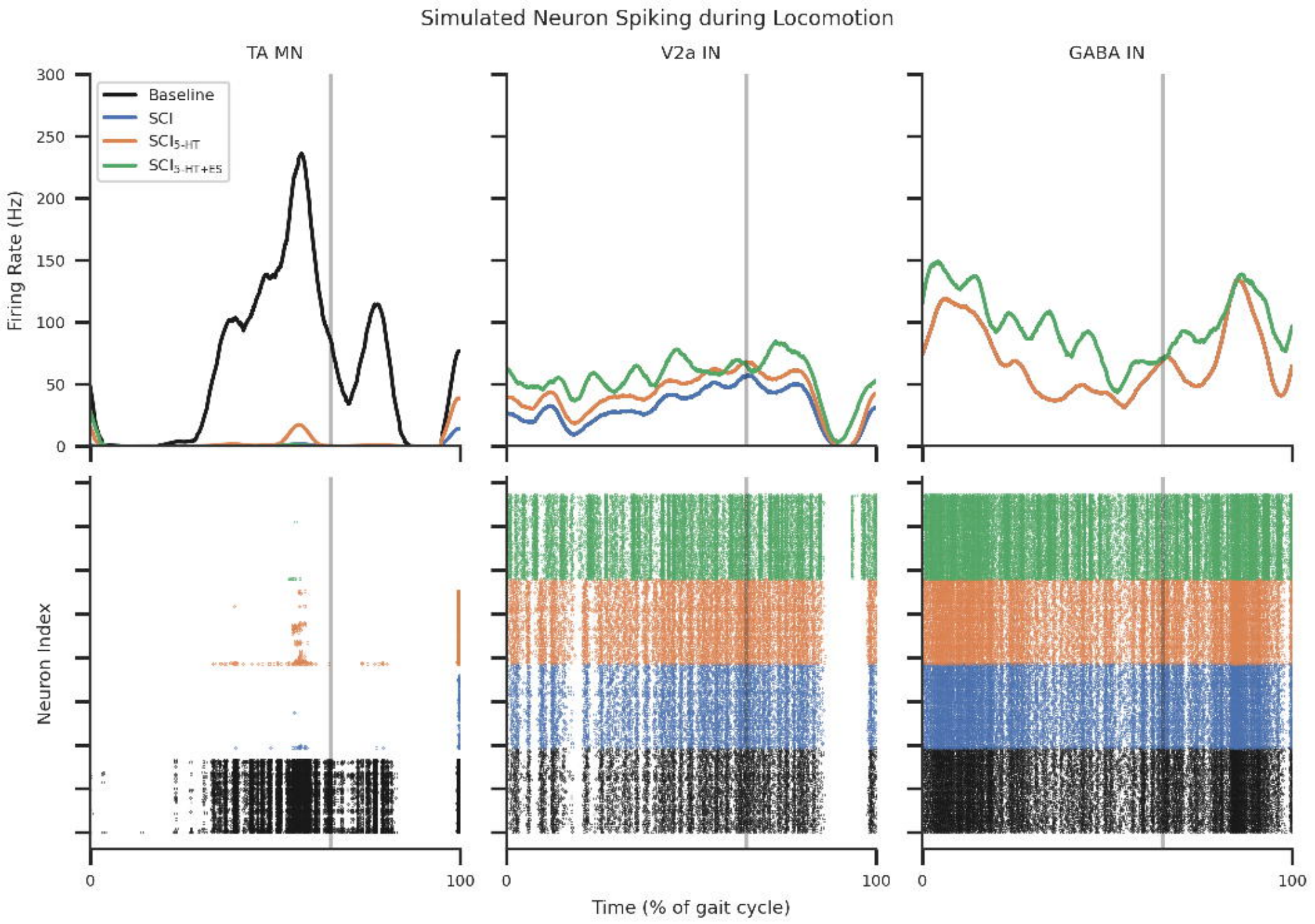
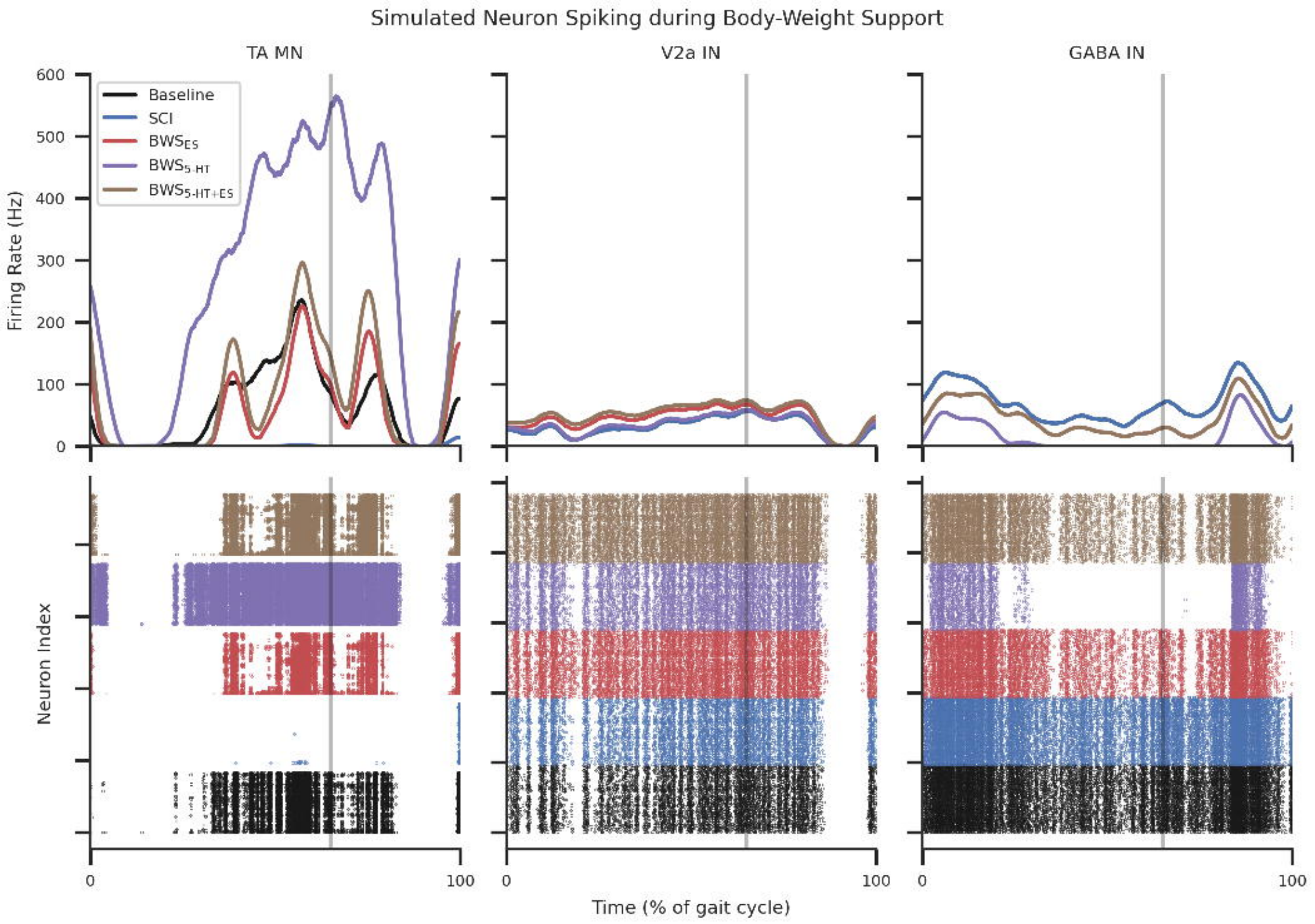
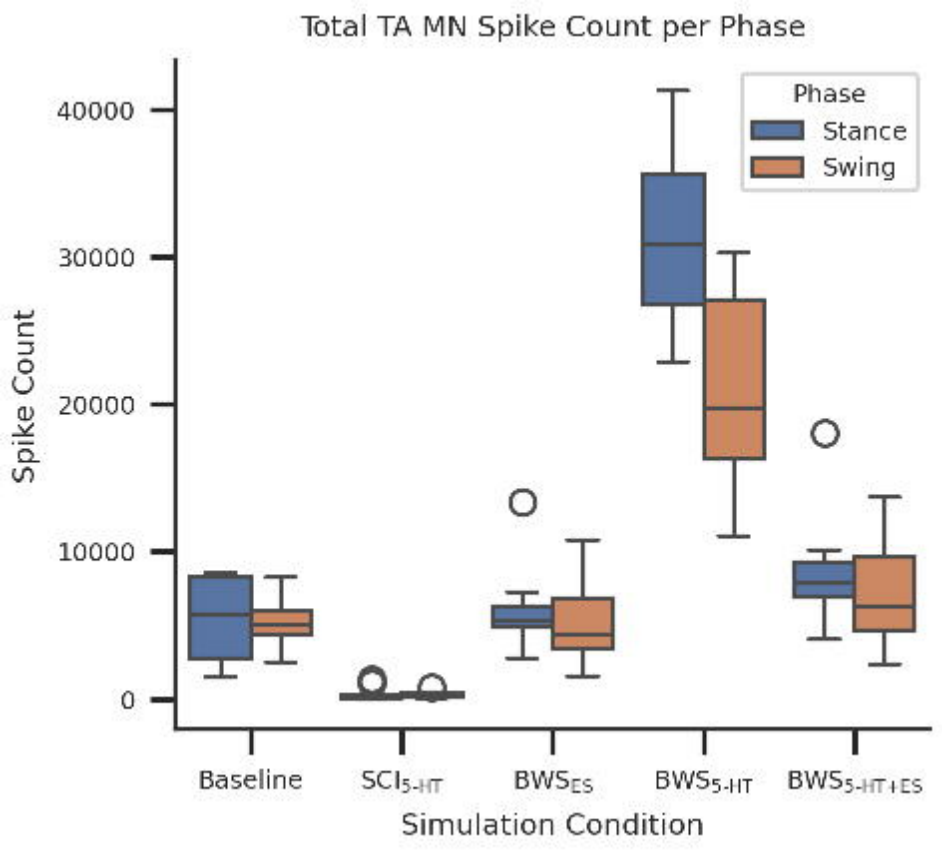
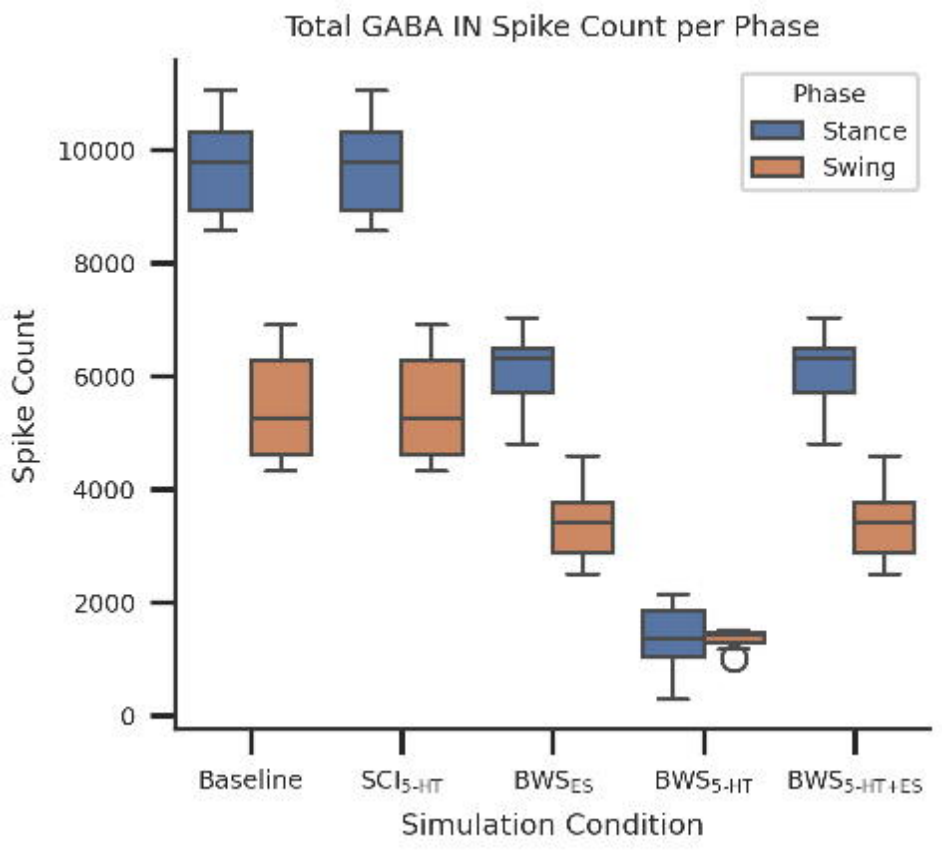

Simulated Baseline and SCI Flexor Firing Rates
Baseline and SCI
Baseline
SCI
Firing Rate (Hz)
150
100
50
0
SCI
Firing Rate (Hz)
8
6
4
2
0
0
20
40
60
80
100
Time (% gait cycle)

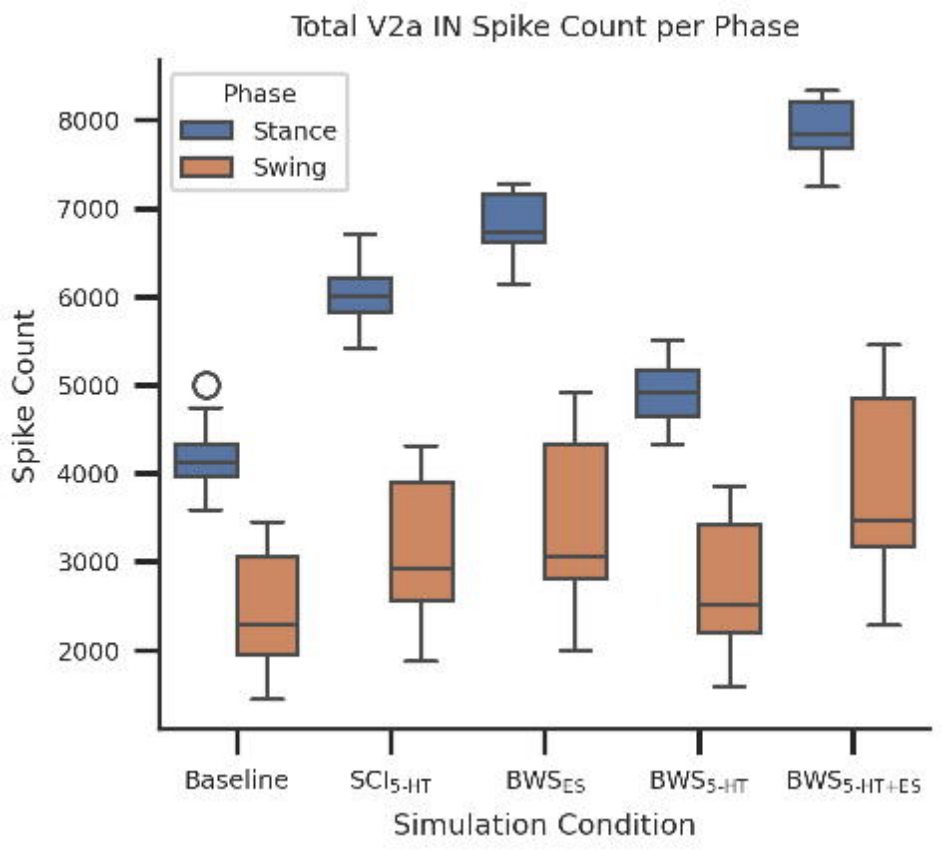

Simulated GABA Presynaptic Inhibition
MN Membrane Voltage
mV
−25
−50
−75
Baseline
SCI
GABA Scaling Factor
a.u.
0.5
0.0
Spiking Activity
Simulation Condition
0
100
Time (% gait cycle)

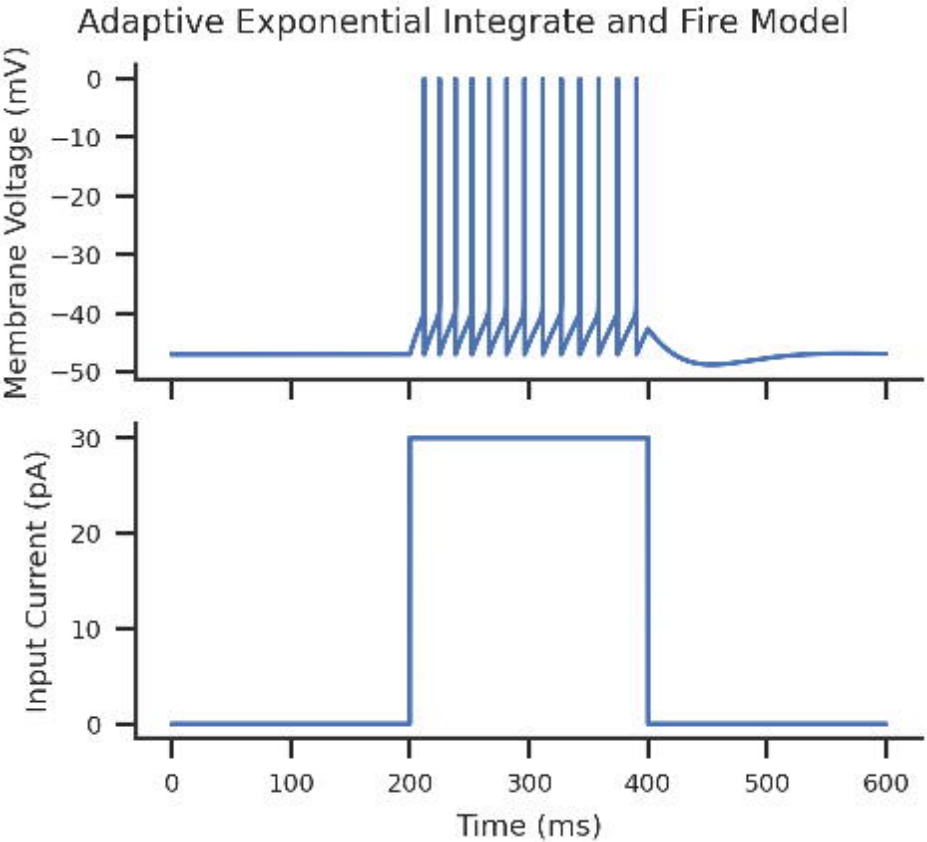

Simulated Neuron Spiking during Locomotion
TA MN
V2a IN
GABA IN
Baseline
SCI
SCI5-HT
SCI5-HT+E5
Firing Rate (Hz)
300
250
200
150
100
50
0
Neuron Index
0
100
Time (% of gait cycle)

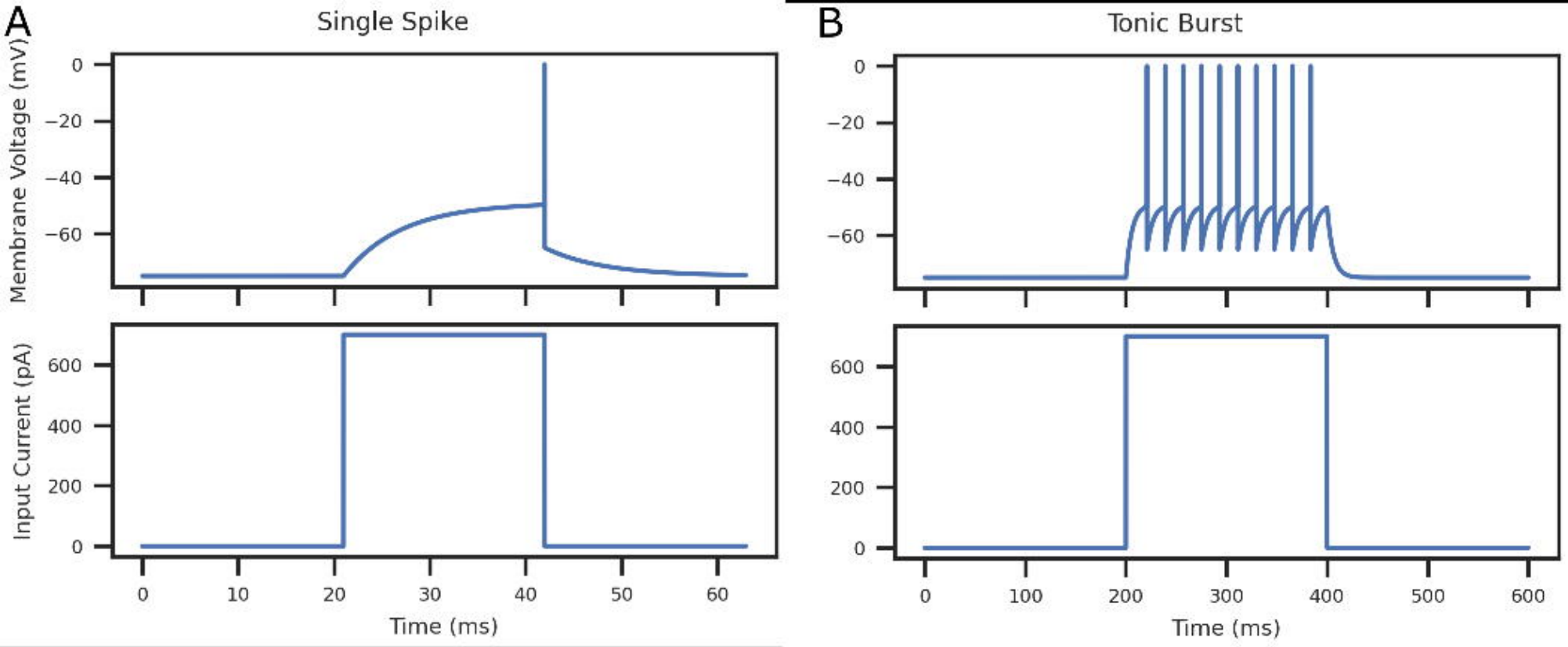

Simulated Neuron Spiking during Body-Weight Support
TA MN
V2a IN
GABA IN
Baseline
SCI
BWS$_{ES}$
BWS$_{5\text{-}HT}$
BWS$_{5\text{-}HT+ES}$
Firing Rate (Hz)
600
500
400
300
200
100
0
Neuron Index
0
100
Time (% of gait cycle)


Total TA MN Spike Count per Phase
Phase
Stance
Swing
Spike Count
40000
30000
20000
10000
0
Baseline
SCI5-HT
BWSES
BWS5-HT
BWS5-HT+ES
Simulation Condition


Total GABA IN Spike Count per Phase
Phase
Stance
Swing
Spike Count
10000
8000
6000
4000
2000
0
Baseline
SCI5-HT
BWSES
BWS5-HT
BWS5-HT+ES
Simulation Condition


Total V2a IN Spike Count per Phase
Phase
Stance
Swing
Spike Count
8000
7000
6000
5000
4000
3000
2000
Baseline
SCI5-HT
BWSES
BWS5-HT
BWS5-HT+ES
Simulation Condition


Adaptive Exponential Integrate and Fire Model
Membrane Voltage (mV)
0
−10
−20
−30
−40
−50
Input Current (pA)
30
20
10
0
0
100
200
300
400
500
600
Time (ms)


A
Single Spike
Membrane Voltage (mV)
0
−20
−40
−60
Input Current (pA)
600
400
200
0
0
10
20
30
40
50
60
Time (ms)
B
Tonic Burst
0
−20
−40
−60
600
400
200
0
0
100
200
300
400
500
600
Time (ms)