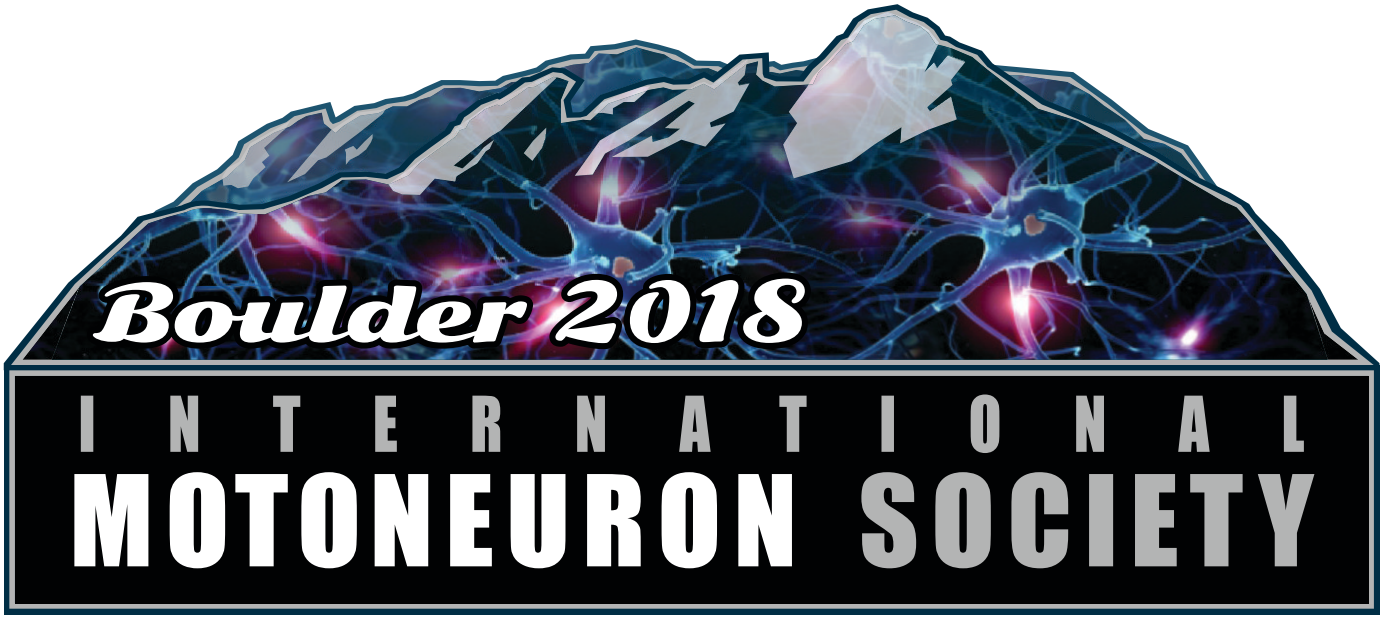
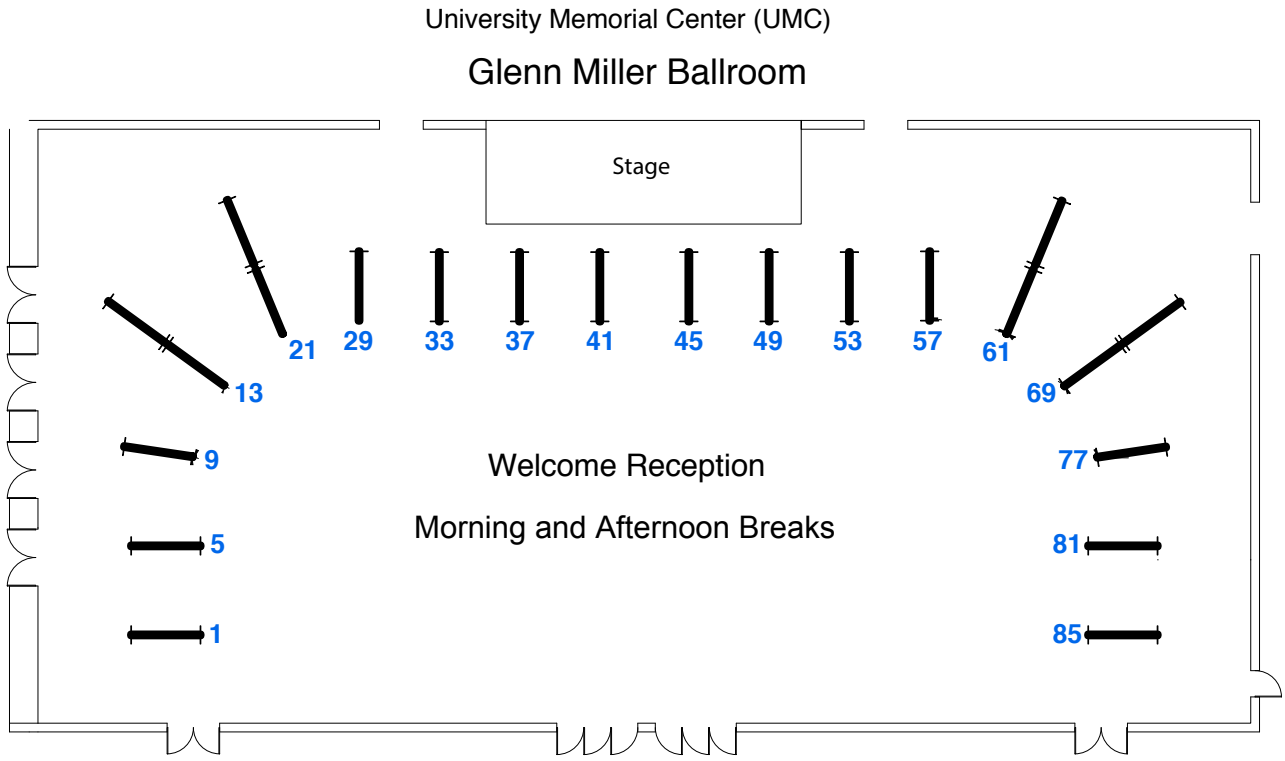


11th Biennial Meeting

June 11-14, 2018

University of Colorado Boulder

POSTER BOARD LAYOUT



Poster Instructions

- Size – 48 in x 48 in (115 cm x 115 cm)
- Mount your poster at the assigned number (see the following list for poster numbers)
- There will be 4 posters on each poster board (4 ft x 8 ft)
- Your poster should be mounted during the morning break on Monday and removed at the end of the day on Wednesday
- Poster presenters are asked to be available at their poster during the indicated session:
    - Session A – Monday, morning break
    - Sessions B and C – Monday, lunch
    - Session D – Monday, afternoon break
    - All posters – Monday, Welcome Reception
    - Sessions F and G – Tuesday, lunch
    - All posters – Tuesday, 1:30 – 4:00 pm
    - Session H – Wednesday, morning break
    - Session I – Wednesday, lunch
    - Session J – Wednesday, afternoon break

  Of course, poster presenters are welcome to be available at other times as well.

2018 Poster Abstracts

Poster Session A

1. Multi-channel functional electrical stimulation increases the duration and intensity of cycling after a spinal cord injury

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Restoration of motor function after spinal cord injury (SCI) using functional electrical stimulation (FES) has not gained widespread use, in part, due to rapid fatigability of evoked contractions. This fatigability is largely due to the non-physiological way that motor units are recruited by FES, drastically reducing the maximal duration and intensity of FES sessions. Multi-channel FES (multi-FES) distributes stimulation among multiple, spatially distributed electrodes with the aim of reducing motor unit firing rates to within their natural range. Therefore, the aim of this study was to determine if multi-FES reduces contraction fatigability of the quadriceps compared to a conventional commercially-available type of FES (Con-FES) during leg cycling after a SCI. 14 participant with a motor complete SCI completed 2 FES leg-cycling sessions on a Restorative Therapies RT300 cycle ergometer on separate days. Con-FES was delivered between two electrodes over the quadriceps muscle while multi-FES rotated stimulation pulses between 4 electrodes with a common anode. Cycling trials consisted of 1-min passive, 5-min motor assisted, followed by unassisted FES-cycling until fatigue (cadence <15 rpm). A 5-min rest period was followed by 1-min passive cycling and unassisted FES-cycling until fatigue. Outcome measures included ride-time, which was the combined time of unassisted cycling, and average power output. Measures of peak twitch torque (PTT) and torque-frequency relationships were assessed isometrically in the right quadriceps via strain gauge prior to and immediately after each cycling trial. Ride time (477±575 s vs 165±177 s) and average power output (1.1±0.3 W vs 0.65±0.3 W) were significantly increased during multi-FES compared to conventional FES (p<0.05). PTT data indicates multi-FES cycling reduces the force generating capacity of the quadriceps more than conventional FES (p<0.05). Multi-FES reduces fatigability of electrically-evoked contractions during leg cycling after SCI leading to increased duration and intensity of FES-cycling. Generating fatigue-resistant contractions which increase the physiological load of FES-cycling sessions may improve the effectiveness and adoption of FES-based rehabilitation.

2. Do individuals develop a fast motor axon phenotype following a SCI and is that altered by FES-based exercise?

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Individuals who experience paralysis following a spinal cord injury, exhibit atrophy of skeletal muscle accompanied by a decrease in the relative amount of slow and increase in fast IIx myosin isoforms. Long-term functional electrical stimulation (FES) can - to some extent - reintroduce slower myosin isoforms (e.g., IIa). It has been suggested that the motor axons may also exhibit adaptations resulting from the diminished impulse activity. The objective of this study was to determine if individuals with a spinal cord injury develop motor axon phenotypes that match the *fast* muscle phenotype and whether this is altered by participation in FES-based exercise. Motor axon phenotype was measured using nerve excitability testing. Experiments were done in rats to test for differences in nerve biophysics

between the tibialis anterior (fast) and soleus (slow) muscles. Fast motor axons in the rat have results consistent with: decreased Ih current, decreased internodal K-slow, and increased paranodal K-fast currents. A cross-sectional sample of 13 individuals attending a community FES-cycling program participated in nerve excitability tests of the common peroneal and median nerves. Four individuals were found to have inexcitable peroneal nerves. Individuals with incomplete injuries had test results similar to our normative database whereas individuals with complete injuries displayed a range of atypical features, some of which were consistent with the fast motor axon phenotype seen in the rat. Two cases were compared in detail: >4 years since injury, motor complete, mid-thoracic level injury with comparable amounts of spasticity. Both individuals were long-term FES cyclers, but only one included routine stimulation of the tibialis anterior. This individual had nerve excitability indices that were indistinguishable from controls while the other individual had a wide range of atypical indices, including those indicating increased membrane conductance and decreased internodal K-slow currents. These preliminary results suggest that motor axons develop atypical features after SCI that share some similarities to the fast phenotype in rats and that these features are absent in individuals with targeted FES.

3. Sustained muscle tone and muscle spasms after spinal cord injury: an expression of Henneman's size principle

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Spinal cord injury (SCI) results loss of motor function and sensory function later followed by involuntary muscle contractions. The involuntary muscle contractions may generate a chronic increase in muscle tone and sudden and temporally-limited muscle contractions or spasms. The neuronal mechanisms for these aberrant motor responses are not well understood.

Here we used a mouse model of chronic SCI with a sacral lesion to examine the development of the aberrant motor responses. We find that aberrant motor responses develop in tail muscles 3-4 weeks after spinal transection at S2 and stabilize 6-8 weeks after transection. The motor responses are characterized by sustained tonic activity and spasms. The sustained tonic activity is generated by activity in small sized tail motor units (MUs) that are recruited permanently 6-8 weeks after SCI. In contrast, spontaneous muscle spasms, are supported by activation of large sized tail MUs. The spasms are superimposed on the sustained tonic activity.

We further functionally characterized the recruitment of small and large MUs in tail muscles using optical stimulation of motor neuron axons in *Chat^{Cre} ; R26ChR2*. Optical activation of channelrhodopsin expressing motor axons in animals without SCI showed that small motor units are recruited by low light intensity while larger motor units where recruited by increasing light-intensity. The light stimulation, therefore, evokes a recruitment pattern that strictly follows Henneman's size principle. Using, light stimulation *Chat^{Cre}; R26ChR2* in spinalized animals showed that the firing frequency of small motor neurons could be increased leading to stronger sustained activity while stimulation of larger MUs lead to spasm-like contractions.

In conclusion, our study shows that the development of aberrant motor responses after SCI have two components – sustained muscle tone and spasms - that that are supported by recruitment of different sized motor units. The recruitment follows Henneman's size principle and orderly (de)recruitment of motor units with optical stimulation may provide possibilities to inhibit muscle contraction in a graded manner.

4. Targeted nanoparticle strategy for cervical spinal cord injury

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Spinal cord injury (SCI) commonly affects cervical segments and results in impairment of respiratory function due either to disruption of descending drive or frank injury to phrenic motor neurons that innervate the diaphragm muscle. The current gold standard of treatment for these patients is ventilatory support and surgical stabilization of the damaged vertebrae, neither of which address disrupted premotor drive or damaged motor neurons. It is therefore necessary to address this gap by developing an effective targeting strategy for treatment after injury. Toward this end we are developing a targeting strategy that utilizes a mesoporous silica nanoparticle encapsulated in a lipid bilayer (protocell) with the surface modified to include cholera toxin B (CTB). These CTB protocells are designed to target motor neurons and deliver an intracellular therapeutic cargo. The efficacy of these CTB protocells in motor neurons was tested using a hybrid neuronal cell line (NSC-34), which can approximate mouse motor neurons after differentiation. In NSC-34 cells, we demonstrated that CTB protocells displayed properties of effective targeted therapeutic delivery, including facilitated uptake by endocytosis and lack of cytotoxicity. Subsequently in a rat model, we found that after intrapleural injection, CTB protocells was detected within presynaptic terminals of the phrenic nerve (75-80% efficiency) as well as in phrenic motor axons. These results indicate that CTB protocells can be utilized for retrograde transport and targeted therapy to phrenic motor neurons. Such a novel targeted therapy may be effective in reducing morbidity and mortality in patients with SCI.

5. Diaphragm muscle function following contusion injury-induced phrenic motor neuron loss

Khurram OU, Fogarty MJ, Rana S, Vang P, Sieck GC, Mantilla CB.

Departments of [1]Physiology & Biomedical Engineering, [2]Neurobiology of Disease, and [3]Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN
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Mid-cervical spinal cord contusion injury results in tissue damage, disruption of spinal pathways, and motor neuron loss. Phrenic motor neurons located in C3-5 segments of the cervical spinal cord innervate the diaphragm muscle (DIAm), and unilateral C4 contusion results in loss of 40-50% of motor neurons ipsilateral to the injury (~25% of the total motor neuron pool). Transdiaphragmatic pressure (Pdi), which is a surrogate DIAm force *in vivo*, was measured across motor behaviors over time after unilateral C4 contusion injury. Maximum Pdi (Pdi_{max}) was elicited by bilateral phrenic nerve stimulation at 7 days post-injury. Importantly, ventilation requires only 10-20% of Pdi_{max} and even repeated inspiratory efforts against an occluded airway (~40% Pdi_{max}) can be accomplished by recruitment of only fatigue-resistant motor units. We hypothesized that following C4 mid-cervical contusion injury Pdi_{max} is reduced, but ventilatory behaviors are accomplished without deficit. In support of our hypothesis, we observed that Pdi_{max} was reduced by ~25% after C4 mid-cervical spinal cord contusion injury compared to a laminectomy control group. This decrease in Pdi_{max} is consistent with the extent of phrenic motor neuron loss following contusion injury. We also found that during both eupnea (quiet breathing) and breathing stimulated by 10% O_2 (hypoxia) and 5% CO_2 (hypercapnia) Pdi generation was unimpaired by C4 mid-cervical spinal cord contusion injury, again consistent with the lower force requirement of these ventilatory motor behaviors. After injury, DIAm electromyography (EMG) amplitude and central drive during airway occlusion are increased both ipsilateral and contralateral to the side of injury, while Pdi generation is unimpaired. Thus, to generate a given Pdi, more EMG activity is necessary post-injury. Collectively, these findings suggest that recruitment of higher-threshold motor units and/or increased discharge frequency of surviving motor neurons post-injury may allow for compensation after phrenic motor neuron loss.

6. Altered sensory gating during voluntary activity in humans with spinal cord injury

Lei Y, Perez MA.

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Spinal cord injury (SCI) often disrupts the integrity of afferent axons projecting through the spinal cord dorsal columns to the brain. However, the extent to which afferent input is gated along the ascending sensory pathway after SCI remains largely unknown. Here, we used electroencephalographic recordings over the somatosensory cortex (S1) and electrical stimulation of the ulnar nerve at the wrist to examine somatosensory evoked potential (SSEP) components reflecting subcortical (P14) and cortical (N20 and P33) contributions and intracortical inhibition in the S1 at rest and during 30% of isometric maximal voluntary contraction (MVC) into index finger abduction. At rest, SSEPs had prolonged latencies and decreased amplitudes in SCI compared with control subjects. We also found that the amplitude of all SSEP components were suppressed more in SCI than in control subjects during 30% of MVC. Intracortical inhibition suppressed the amplitude of the N20 in SCI subjects to a larger extent than controls, suggesting a cortical origin for this effect. To probe the functional relevance of altered sensory gating following SCI, we examined somatosensory temporal discrimination threshold (STDT) by measuring the shortest time interval to perceive a pair of electrical stimuli. STDT was increased in SCI compared with control subjects. Our novel findings demonstrate pronounced gating of sensory input at subcortical and cortical regions in humans with SCI compared with controls. Enhanced sensory gating during voluntary activity might increase discrimination threshold after SCI.

7. Phrenic motor neuron size dependent neuroplasticity of glutamatergic neurotransmission following cervical spinal cord injury

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Departments of [1]Physiology & Biomedical Engineering and [3]Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN

Among patients with spinal cord injury (SCI), >50% involve the cervical spinal cord, with many cases resulting in diaphragm muscle (DIAm) paralysis and impaired ventilation. Importantly, most SCIs are incomplete with sparing of descending excitatory inputs to phrenic motor neurons (PMNs). Unilateral C2 hemisection (C2SH) is an animal model of incomplete SCI widely used to examine neuroplasticity in the neuromotor control of breathing following injury. Excitatory premotor drive to PMNs emanates predominantly from the ipsilateral medulla, is primarily glutamatergic (Glu), and is mediated by various receptor subtypes. In recent studies, we found that the amplitude of respiratory-related DIAm activity (generally accomplished by recruitment of smaller PMNs) is reduced after C2SH, while DIAm EMG activity during higher force, non-ventilatory behaviors (generally recruitment of larger PMNs) is only minimally impaired. Gradual recovery of rhythmic DIAm activity ipsilateral to injury is evident over time, consistent with neuroplasticity and strengthening of spared synaptic inputs to PMNs. Thus, we hypothesized that there are size dependent differences in the cellular mechanisms underlying PMN neuroplasticity after C2SH. To address this hypothesis, AMPAR and NMDAR mRNA expression in retrogradely-labeled PMNs was measured using RNAscope. Glu presynaptic input was assessed by immunohistochemistry for VGLUT1 and VGLUT2. We found that immediately following C2SH (by 3 and 7 days), there was a pronounced reduction in both AMPAR and NMDAR mRNA expression in smaller PMNs as well as a substantial reduction in Glu synaptic input. In contrast, AMPAR and NMDAR mRNA expression and Glu synaptic input in larger PMNs was unaffected. These results indicate a more pronounced impact of C2SH on smaller PMNs. Subsequently by 21 days post-C2SH, we observed a marked increase in AMPAR and NMDAR mRNA expression as well as an increase in Glu synaptic input in smaller PMNs. These results are consistent with the involvement of Glu synaptic transmission in the spontaneous recovery of ipsilateral DIAm EMG activity after C2SH.

8. Novel closed-loop epidural stimulation of the cervical spinal cord promotes forelimb function after a severe spinal cord injury

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[1]Healthy and Rehabilitation Sciences, Physical Therapy, [2]Neurobiology and Behavior, Stony Brook University, Stony Brook, NY

Lack of independence resulting from impaired upper limb function substantially compromises the quality of life of persons with a cervical spinal cord injury (cSCI). Neuromodulation of the spinal cord using epidural stimulation (ES) of the lumbosacral cord in humans has led to the volitional control of lower limb movements after a clinically complete SCI. Whether ES of the cervical spinal cord can restore forelimb motor impairments after a cSCI remains unknown**.** Compelling evidence now indicates that the effect of electrical stimulation is functionally more meaningful when the stimulation pulse is delivered in response to an endogenous neural drive. Recently, we developed a closed-loop ES strategy that delivers cervical **ES t**riggered by onset of spiking activity within the EMG burst **(tES)** during voluntary movement. The underlying premise is that the stimulation pulse delivery linked to the timing of ongoing endogenous neural drive will significantly enhance voluntary attempts to move. The main purpose of this study is to test feasibility of tES in rats with a severe cSCI and determine if tES training will restore forelimb function. Experiments were performed on six adult rats. After going through EMG and ES implant procedures, rats were hemisected at the C4 spinal segment. Training with tES involved ES delivery after the injury for 6 hours per session, for 6days a week for 3 months during volitional attempts to move in their home-cage. EMG and behavioral data were collected to assess recovery of forelimb function at several time points during the training period. Our preliminary data indicate that tES can readily be implemented in the rat's home cage without tester supervision. Our data also provide evidence that tES enhances forelimb locomotor function as well as a variety of complex patterned movements of the paralyzed forelimb after a hemisection injury. The significance of this work is that tES will have major implications for use as a neuroprosthetic home-therapy tool for restoration of upper limb function after neurological dysfunction.

9. Synthetic THC to reduce SCI-induced spasticity

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Physical Therapy and Human Movement Sciences Department and Department of Physiology, Northwestern University, Chicago

Spinal cord injuries disrupt messages between the brain and the body distal to the injury. This results in paralysis below the injury level and makes daily function very difficult. In addition, most people with spinal cord injury develop hyperreflexia and involuntary muscle contractions, or spasms, that cause even more movement dysfunction as well as pain, contractures, and safety issues.

Anecdotal evidence from patient reports list marijuana as a very effective drug to decrease spasms, but this has not been systematically tested. In this study, we aim to test whether the administration of a synthetic THC, Marinol, reduces spinal reflexes *in vivo* and *in vitro*, and would therefore decrease spasms post injury. If so we can further investigate the therapeutic mechanism to develop a more specific future pharmacotherapy for patients who suffer from SCI.

For these studies, we used a chronic transection mouse model of SCI. We compared electrical outputs from muscle and nerve tissue before and after administering baclofen or Marinol in the SCI mice. To compare how muscle contractions were impacted by our drug interventions we tested spasticity *in vivo* by recording the flexor withdrawal EMG response to an electrical stimulus three months post injury. To directly measure the effects of baclofen and Marinol on the spinal reflexes, we removed the sacral section of the spinal cord, stimulated the dorsal roots, and then recorded the ENG response through the ventral roots.

Anecdotal accounts claim that marijuana is effective at reducing spasticity following spinal cord injury. This study aimed to systematically determine whether THC has a significant effect on spasticity *in vivo* and *in vitro* and whether THC signaling pathways are a potential therapeutic target for patients with SCI.

Poster Session B

10. Differential effects of botulinum toxin on reflex and voluntary activity of upper arm muscles in stroke survivors based on surface EMG recordings.

Afsharipour B[1,2], Chandra S[1,2], Rymer WZ[1,2], Suresh NL[1,2]

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Botulinum toxin (BT) reduces spasticity post stroke through chemical denervation of motor endplates in spastic muscles. In addition to α MN denervation, animal studies show γ MN denervation may happen as well in BT injected muscles. However, in human, little is known regarding the time course effect of BT on muscle fibers innervated by α vs. γ MNs (extrafusal vs. intrafusal). Since voluntary activity and stretch reflex evoked responses are modulated via α and γ MNs respectively, we compared surface electromyogram signals (sEMG) during isometric voluntary activity with stretch reflex responses to establish comparative time course of BT effects in the Biceps Brachii (BB) of a stroke survivor. We hypothesize that differences in time course for voluntary and reflex activation following BT injections would provide evidence of BT actions on gamma innervation.

We used 16x8 sEMG grids to record the BB's activity during submaximal sustained isometric elbow flexions, and during randomized tendon taps on the bicipital tendon. We collected data before and after BT injection for up to 18 weeks. Root-mean-square (RMS) maps for steady state forces period were computed. For the reflex responses, we recorded the RMS reflex response of each tendon tap (TT) and computed RMS vs. TT force curve.

At 2 weeks after the BT-injection, RMS voluntary EMG maps were substantially reduced. Subsequently, we observed a non-uniform recovery of muscle activity, faster in proximal-distal direction than medial-lateral. Recovery began at 4 weeks and full recovery occurred after 6 weeks. For the reflex responses, there was a significant decrease in evoked potentials at 4 weeks post-BT that lasted up to 18 weeks. There is thus a differential effect of BT on voluntary and reflex activity after BT-injection, implying a time difference in the recovery of α and γ MN innervation to extrafusal and intrafusal fibers.

11. **Effect of botulinum-toxin on force-EMG relations of biceps brachii in stroke** survivors

Chandra S[1,2], Afsharipour B[1,2], Rymer WZ[1,2], Suresh NL[1,2].

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[2]*Department of Physical Medicine and Rehabilitation of Northwestern University*

Botulinum-toxin (BT) is often utilized by physicians to reduce muscle spasticity in stroke survivors. This toxin is administered to reduce hyperactivity of the spastic muscle, by blocking neuromuscular transmission, affecting both voluntary muscle activation and control. We hypothesize that Botulinum-toxin affects force-EMG (surface electromyogram) relations due to non-uniform changes in motor unit(MU) composition, resulting in alterations in motor unit control in the injected biceps brachii muscle.

Four stroke survivors were tested. Participants were seated in a Biodex, Inc. chair with the forearm cast from elbow to the wrist and fixated to a ring-mount interface attached to a six degrees-of-freedom load cell (ATI, Inc.). Bipolar sEMG electrodes were placed on the medial and lateral biceps brachii and triceps muscles and were used to record an isometric, non-fatiguing elbow flexion

contraction. Visual feedback of a trapezoidal force trajectory was provided to the subjects. The maximum voluntary contraction (MVC) was recorded at each session, followed by designated contraction levels varying from 30% to 50% of the MVC. The force-sEMG relation was then analyzed across all tested force trials. We tested all subjects for one pre-BT session and biweekly tests for 12 weeks post BT.

Until week 4, along with force, the peak to peak sEMG amplitude of the affected muscle also showed significant decreases in value in the post BT sessions. There was a consistent increase in the force-sEMG slope for the post BT sessions compared to baseline recordings (pre-BT session) in this time period. Our data suggest control of the muscle has changed such that there is relatively greater MU recruitment for similar force values. Concurrently recorded motor unit data would provide further insight, subsequent to analysis.

12. Accumulated neural adaptations in response to non-paretic hand exercise to task-failure

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We previously observed acutely reduced ipsilesional hemisphere (IH) intracortical inhibition in response to non-paretic hand exercise to task-failure in chronic stroke survivors. Effects were sustained for up to 4hours and accompanied by facilitation of paretic hand motor performance. Here we investigated whether these effects accumulate over repeated sessions. We studied 10 individuals with chronic stroke (upper-extremity Fugl-Meyer assessment: 26-65/66) who performed submaximal non-paretic hand isometric powergrip to task-failure twice weekly for 4weeks. We used transcranial magnetic stimulation (TMS) to investigate short intracortical inhibition (SICI) and the Box and Blocks Test (BBT) to measure manual dexterity. At each session we tested powergrip maximal voluntary contraction (MVC), BBT, and TMS prior to and immediately following task-failure. Results demonstrated both neurological and behavioral effects. Neurological effects. IH SICI was induced in 8/10 participants revealing two distinct patterns: a) 4 individuals showed baseline disinhibition, pre-exercise SICI increased (i.e., more inhibition) significantly ($p=0.046$) over 8 sessions; b) 4 individuals showed baseline inhibition (i.e., expected response), pre-exercise SICI did not change significantly over sessions. At study baseline, SICI differed significantly between groups ($p=0.034$), but no difference was detected at session 8 ($p>0.05$). Behavioral effects. In most participants, behavioral improvements (i.e., MVC, BBT) in the non-exercised, paretic hand exceeded those in the exercised, non-paretic hand. BBT improvement over sessions was greater in lower-functioning compared to higher-functioning individuals ($r^2=0.71$, $p=0.002$). We previously observed a relationship between severity of motor impairment and reduced SICI (i.e., disinhibition, deficient $GABA_A$ regulation) in chronic stroke. While the importance of GABAergic activity to motor control and dexterity is known, its role in motor recovery following stroke remains unclear. Our results suggest IH $GABA_A$-mediated brain circuit function can be normalized non-invasively. Effects of non-paretic limb exercise to task-failure appear to accumulate over repeated sessions positively impacting both $GABA_A$-mediated circuits and paretic arm motor function.

13. The effects of a single session of chiropractic care on strength, cortical drive, and spinal excitability in stroke patients

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The objective of this study was to investigate whether single session of chiropractic care could increase strength in weak leg muscles in chronic stroke patients. Maximum voluntary contractions (strength) of the plantar flexors, soleus evoked V-waves (cortical drive), and the H-reflexes were recorded in 12 chronic stroke patients with lower limb muscle weakness using a randomized controlled crossover design. Outcomes were assessed pre and post a chiropractic intervention and a passive movement control. Repeated measures ANOVA was used to asses within and between group differences. Significance was set at $p \leq 0.05$. Following the chiropractic intervention there was an increase in strength ($F(1,11) = 14.49, p<0.01$; avg 64.2%±78.1%, $p=0.03$) and V-wave/Mmax ratio ($F(1,11)=9.67, p=0.01$; avg 54.0%±65.2%, $p=0.04$) compared to control. There was a strength decrease of 26.5%±15.5% ($p<0.01$) and a non-significant 12.1%±13.8% decrease in V/Mmax ratio($p=0.07$) after the control. There were no other significant differences. A single session of chiropractic care in stroke patients resulted in increased lower limb strength. An increase in V/Mmax ratio combined with no significant changes in H-reflex parameters suggests this increased strength is likely modulated at a supra-spinal level. Further research is required to investigate the longer term and potential functional effects of chiropractic care in stroke recovery.

14. Stroke-related changes in motor unit firing behavior and global surface EMG during fatiguing contractions

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Individuals with chronic stroke have impaired rate coding and recruitment strategies during brief sub-maximal contractions that may contribute to impaired motor performance during repeated sub-maximal fatiguing contractions. Understanding the relationship between paretic motor unit firing behavior and the quality of whole muscle activation may provide insight into stroke-related changes in neuromuscular fatigue. Using multichannel surface electromyography, we quantified global activation and motor unit firing rates of the vastus lateralis muscle during intermittent, isometric fatiguing contractions of the knee extensors in controls (N=9) and participants with chronic stroke (N=10). During the fatiguing protocol, individuals with stroke had similar task duration (15.30±8.23 cycles) as controls (13.67±11.50 cycles), and the percent reductions in MVC was similar for both groups (control:58.83 ±12.39%, stroke:65.70±12.66%, P=0.554). When comparing the first to the last contractions of the fatiguing protocol, the control subjects had a larger increase in motor unit firing rates (12.94±1.74 Hz vs. 14.89±2.22 Hz) compared to the stroke group (10.82±1.86 Hz vs. 11.20±1.57 Hz, p=0.015). From the global surface EMG measurements, the controls had a larger decrease in mean frequency (77.85±14.64 Hz vs. 66.18±16.18 Hz) as compared to those with stroke (69.2±14.33 Hz vs. 67.74±13.03 Hz, p=0.045). On average, controls had a greater increase in mean RMS (first cycle: 37.94±20.94 μV vs last cycle: 54.94±37.72 μV) than individuals with stroke (first cycle: 31.80±29.96 μV vs last cycle: 45.74±47.91 μV) between the first and last contraction. Modified entropy, a metric for the

homogeneity of muscle activation, had a main group effect as the control group (5.66±0.03) was higher compared to the stroke group (5.20±0.04, p=0.042), but there was no change in entropy across contractions for either group. Individuals with stroke demonstrate decreased ability to modulate firing rates and global muscle activation as compared to controls which may contribute to alterations in motor performance during fatiguing contractions.

15. Non-paretic hand exercise to task-failure modulates ipsilesional hemisphere and paretic hand function in chronic stroke

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We previously observed non-paretic hand exercise to task failure (TF) increased cortical excitability in the *non-exercised* ipsilesional hemisphere (IH) and paretic hand maximal voluntary contraction (MVC) force in persons post-stroke. Here, we sought to determine how intracortical inhibition and interhemispheric inhibition (IHI) contribute to these previously-observed effects and whether they influence dexterity as well as force production capacity. We studied 11 individuals with chronic stroke (upper-extremity Fugl-Meyer assessment: 28-66/66) who performed repeated submaximal non-paretic hand isometric powergrip to TF. We used transcranial magnetic stimulation (TMS) to investigate short intracortical inhibition (SICI) and ipsilateral silent period (iSP) and the Box and Blocks Test (BBT) to measure dexterity. Powergrip MVC, BBT, and TMS were tested at baseline, immediately post-TF, and every 45 min until 4hours post-TF. IH SICI was induced in all participants revealing two distinct patterns: a) baseline inhibition (n=6) (i.e., expected response) – in these individuals, SICI revealed a marked (140%, p=0.026), transient disinhibition immediately post-TF that returned to baseline by 45 min post-TF (p's>0.05); b) baseline disinhibition (n=5) – in these individuals SICI increased (30%) immediately post-TF and remained increased (i.e., inhibited) for the full 4hour recovery period (p=0.025). At 4hours post-TF, IH iSP was significantly increased compared to baseline (p=0.042) reflecting increased Ipsilesional-to-Contralesional IHI. Paretic hand BBT improved in 9/11 participants (0.66-159%) at ≥1 point post-TF. The magnitude of BBT increase was associated with UE FMA (p=0.03), suggesting people with more severe motor impairment reveal greater behavioral facilitation in the paretic hand in response to TF. Systematic, sub-maximal non-paretic hand exercise to task-failure significantly modulates IH activity, normalizing both intracortical circuit function and interhemispheric interactions when disrupted. Persistence of these neuromodulatory effects for at least 4hours potentially offers a therapeutic window during which traditional rehabilitation therapies may be more efficacious, especially for lower functioning individuals post-stroke.

Poster Session C

16. Ontology-based Web Database for Understanding Amyotrophic Lateral Sclerosis (ONWebDUALS): first results of an international project

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Present understanding of the ALS risks factors is incomplete, presumably because they have never been integrated with phenotype-genotype patient profiles. The aim of the presented project is to define specific risk factors in relation to the genotype-phenotype patient's background. For the project we have built a standardized patient questionnaire and an ALS domain ontology representing the body of medical knowledge related to this disorder. The ontology served as a formal basis for the construction of European ALS Web-database. The project started at March 1st, 2015. Since then, consortium members from neurological clinics in Antalya, Hannover, Jena, Lisbon and Warsaw, are interviewing ALS patients on the basis of developed detailed questionnaire. At present the database, hosted by the Nalecz Institute of Biocybernetics and Biomedical Engineering, includes approximately 1000 patients and 500 control subjects. The results of the first analyses include population data, disease characteristics and progression, and potential risk factors such as co-morbidities, occupations or diet. Also, diagnostic path will be analyzed, which includes time lags between first symptoms and diagnosis, numbers and types of specialists involved, the most important laboratory investigations, etc. All results will be also compared between the participating countries. One of the most unexpected findings obtained so far is strikingly low percentage of left-handers among patients (4% compared to 9% in control group).

17. *In Vitro* trauma induces TDP-43 proteopathy and exacerbates motor neuron degeneration in ALS patient iPSC-derived motor neurons

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** denotes equal contribution to this project*

Mild traumatic brain injury (mTBI) appears to be an epidemiological risk factor for Amyotrophic Lateral Sclerosis (ALS). To help address the clinical association of mTBI with ALS, we applied an *in vitro* stretch trauma model to the study of patient-specific motor neurons (MNs) generated from induced pluripotent stem cells (iPSCs). This recently developed trauma system has now been validated to deliver a tunable injury ranging from severe neurodegeneration to milder forms of axonal and synaptic

injury. Briefly, day 4 iPSC-MNs derived from healthy controls, SOD1A4V and C9orf72 mutants underwent stretch injury. A 96 well, custom built, silicone-bottomed plate was lowered, stretching the well membrane over the rims of static metal posts, causing mechanical stress to the cells in the well. Posts were omitted from the post array to create un-stretched control wells within the same plate. The cultures were then fixed 4-72 hours after injury and stained with anti-TDP-43 antibody. We found that MNs from C9orf72, but not healthy controls or SOD1A4V, had abnormally increased TDP-43 in the cytoplasm. This phenomenon is referred to as TDP-43 mis-localization. Interestingly, these results are congruent with the clinical observation that C9orf72, but not SOD1, patients exhibit TDP-43 proteopathy. Additionally, all ALS mutant cell lines exhibited greater vulnerability to degeneration after mild trauma as compared to healthy control MNs. Further studies to elucidate the molecular mechanisms that mediate ALS-specific pathology after stretch injury are currently underway.

18. Motoneurons with differential vulnerability to ALS exhibit differential soma size plasticity

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The neurodegenerative disorder amyotrophic lateral sclerosis (ALS) is a fatal, debilitating motoneuron disease. Alpha-motoneuron type has been correlated with the cell's size, excitability, function, and vulnerability to the disease such that slow motoneurons are more resistant to the disease than fast motoneurons which are more vulnerable in the disease. Importantly, this type-associated motoneuron vulnerability is similar in both familial and sporadic ALS, indicating that this motoneuron vulnerability differential is independent of the cause of the disease, but is rather likely due to factors intrinsic to the motoneuron that render the cell more or less susceptible to toxic events. We examined whether motoneuron size underlies this vulnerability differential, and whether motoneurons change their size in the disease in a way that renders them more or less vulnerable. Morphological studies have reported conflicting data on motoneuron size change from ALS patients and of transgenic mouse models of ALS. These studies have not tracked the motoneuron size changes throughout the disease process in order to examine potential long-term patterns in size changes during disease pathogenesis. To address this question, we measured the soma sizes of α-motoneurons throughout the lifespan of G93A mice using specific immunohistochemical markers. Our results show that α-motoneurons exhibit soma size changes with a time-dependent pattern (i.e., early enlargement, followed by no change, then shrinkage) during the disease process. Additionally, disease-vulnerable motoneurons were found to increase their soma size, whereas disease-resistant motoneurons either reduced or did not change – but did not increase – their soma size. This plasticity differential between disease-vulnerable and disease-resistant motoneurons was confirmed across spinal cord regions, genders, and motoneuron types. In addition, our results show that cell size alone is a poor indicator of the motoneuron type and its vulnerability in the disease.

19. A putative modifier of spinal muscular atrophy, *SERF*, is required for maximal SMN protein abundance and genetically interacts with a *Drosophila melanogaster* model of SMA

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Proximal Spinal Muscular Atrophy (SMA) results from the diminished abundance of the survival motor neuron (SMN) protein. An early comparison of patient genotypes identified the uncharacterized *SERF1/H4F5* gene as a putative genetic modifier of this disease. While phylogenetically well conserved, the biological function of *SERF1* is unknown and its involvement in SMA remains untested. Here we use an established *Drosophila melanogaster* model of SMN-limited SMA to investigate S*erf* function in the natural and disease states. *Drosophila* deleted for the *Serf* gene are viable and fertile but

show accelerated impairment of adult climbing behavior and accumulate greater quantities of polyubiquitinated protein aggregates characteristic of aged tissue. Consistent with its proposed disease association, RNAi knockdown of *Serf* mRNA enhances the reduced size and diminished viability of flies that express weak *Smn* missense mutants. The loss of *Serf* activity lowers *Drosophila* SMN protein abundance without obvious change in the corresponding *Smn* mRNA. Overexpression of *Serf* partially suppresses the small size and impaired mobility of strong *Smn* point mutants that mimic the SMA state and generally increases the amount of residual SMN protein. This study provides the first evidence for *Serf* function in locomotive behavior and experimental validation of the predicted *Serf/Smn* genetic interaction. Our observations suggest a basis for *SERF1* -sensitive SMA severity through Serf1-dependent accumulation of the limiting SMN protein.

20. Abnormal electrophysiology of spinal motoneurons in an adult mouse model of amyotrophic lateral sclerosis at a late stage

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Hyperexcitability is considered an important pathogenic mechanism in motoneuron death in amyotrophic lateral sclerosis (ALS). In ALS animal models, it has been shown that in ALS motoneurons, the hyperexcitability starts in intrinsic properties in early age, and migrates to synaptic properties in adult before obvious motor symptoms present. Less is known about cellular excitability in the later stages of the disease, during which motor symptoms such as paralysis and muscle tremor become obvious. In this study, we measured intrinsic and synaptic excitability in ALS motoneurons at late stage in an ALS mouse model with mutant SOD1 protein (mSOD1-G93A) and clear motor symptoms. Using intracellular recordings with sharp electrode in spinal motoneurons in an *in vitro* whole cord preparation, our data showed that passive membrane resistance and time constants are similar between the mSOD1-G93A motoneurons and their controls. Action potentials were only slightly, but significantly wider during falling phase in the mSOD1-G93A motoneurons. Intrinsic firings induced by a ramp depolarizing current were similar in the two groups of motoneurons by measuring firing numbers during rising and falling phases and maximum firing frequencies. However, serious deterioration in synaptic properties was observed in these mSOD1-G93A motoneurons, in which spontaneous excitatory postsynaptic potentials (EPSPs) were less frequent, and spontaneous oscillatory EPSPs were rare. Electrical stimulation could only evoke smaller mono- and poly-EPSPs and was not able to evoke oscillatory EPSPs even at a high stimulation intensity. However, applications of glutamate receptor agonists were able to depolarize membrane potentials. These data that suggest deterioration in synaptic connection is the major pathological outcome in the mSOD1-G93A motoneurons at late stage, which would have implications for developing therapeutic treatments.

21. Excitability of spinal motoneurons in ALS patients

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Amyotrophic lateral sclerosis (ALS) is a debilitating neurological disorder characterized by the progressive degeneration of upper (pyramidal cells) and lower (spinal motoneurons) motor neurons, leading to death mostly when respiratory functions are altered. Several mechanisms at cellular and subcellular levels have been identified in neurodegeneration among which hyperexcitability involved in excito-toxicity. Several studies have been conducted in animal models to investigate the excitability of spinal motoneurons, and more recently in motoneurons derived from IPS cells in humans. Depending

on the conditions, including the stage of the disease and rest vs. active conditions, motoneurons exhibited hyper-, normo- and hypoexcitability, and larger persistent inward currents (PICs) have been reported. We further addressed this issue in humans by testing motoneuron excitability using the paired motor unit (MU) recording method, and by testing flexor reflex afferent (FRA) reflexes. Single MUs were investigated using intramuscular fine wire electrodes. The subjects were asked to perform weak tonic contractions to isolate in EMG activity, one MU (MU1) of which we studied the instant frequency. After 10 s, the subjects were asked to perform stronger contraction or we triggered tendon vibration at 100 Hz during 5 s, in order to recruit an higher threshold MU (U2). The experiments were performed in tibialis anterior (TA), in vastus medialis (VM), in extensor carpi radialis (ECR) and in triceps brachialis (TB). In TA EMG, we also investigated the reflex responses produced by electrical stimulation salve (14 1-ms duration shocks, 333 Hz) elicited in the sural nerve, between 2 and 6 times the perceptual threshold (5.5 x PT on average), but below the nociceptive threshold. According to previous studies in TA and soleus, we found that U1 frequency was higher at the recruitment of U2 compared to its frequency at the derecruitment of U2, in all the 4 muscles (between 3 and 5 Hz differences, on average). According to the work of M. Gorassini and colleagues, this change in frequency (ΔF) can be used to evaluate non-invasively the synaptic currents in the motoneuron pool; ΔF have been found increased in spastic patients, which has been attributed to enhanced motoneuron excitability and larger PICs. We compared ALS patients to gender-age matched control subjects and we did not find any difference in ΔF between groups, whatever the muscle group and the clinical evaluation (patients exhibited mild or no motor dysfunctions in the investigated muscles; no correlation was found with disease duration). We only observed that U1 frequency was lower in patients which led to smaller ΔF (significant correlation between the U1 frequency and ΔF), compared to controls. In parallel, we tested the FRA reflex in TA, whose long latency component has been found enhanced in spastic patients and attributed to larger PICs (Bussel and Gorassini's work). We did not find any change in the late reflex component in ALS patients; the duration of the FRA reflex was similar in controls and ALS and the root mean square (RMS) analysis gave similar results in both groups. Overall this study did not raise any evidences for motoneuron hyperexcitability and larger PICs in ALS patients. Synaptic activity at the motoneuron level was found normal, or even smaller according to the lower discharge frequency observed in patients. Based on these results, we can only conclude on normoexcitability, with a trend to hypoexcitability, in symptomatic ALS patients.

22. Inhibitory interneurons in SOD1 mouse model of ALS are hypoexcitable

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While motoneuron hyperexcitability has been the focus of much research in ALS, much less is known about the neurons presynaptic to motoneurons, particularly at an early, pre-symptomatic stage. In this study, whole cell patch clamp was performed on inhibitory interneurons in the ventral lumbar enlargement of the spinal cord from 6-12 day old mice. Interneurons were targeted for recording based on the expression of GFP driven by glycine transporter 2 (GlyT2). Mice were bred for experiments by crossing GlyT2 EGFP mice with SOD1G93A high expresser mice. Preliminary results show that inhibitory interneurons are less excitable in SOD1 mice. Persistent inward currents (PICs) are significantly shifted in their voltage dependence (both PIC onset and maximum voltage are significantly more depolarized: PIC onset and peak in wild type interneurons is -51 +/- 5mV and -36 +/- 5mV, respectively while in SOD1 interneurons these values are -47 +/- 4mV and -32 +/- 5mV). Threshold for firing is similarly more depolarized in SOD1 interneurons (-41 +/- 5mV vs -38 +/- 5mV). This suggests that spinal interneurons may fire less frequently, thus leaving spinal motoneurons in SOD1 mice less inhibited.

Poster Session D

23. Regulation of the potassium chloride cotransporter-2 (KCC2) on spinal motoneurons following peripheral nerve injury.

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Following many types of injury, the potassium chloride cotransporter-2 (KCC2), is dysregulated on neurons injured or associated with neurons that have been injured. This change driving forces for GABA and glycine inhibitory synapses and in general increases excitability in the affected neurons and networks. This phenomenon has been described in dorsal horn sensory-associated interneurons following peripheral nerve injury, as well as on motoneurons after spinal cord injury. In these cases, decreased expression of KCC2 was associated with neuropathic pain and spasticity, respectively. KCC2 is also downregulated in motoneurons axotomized in peripheral nerve injuries, but its significance and mechanisms have received less attention. KCC2 downregulation following nerve injuries was first shown in cranial motoneurons of facial, vagus, and hypoglossal nuclei. We confirmed it also occurs in spinal motoneurons and affects mainly KCC2 found on the cell body and proximal dendrite membranes. The regulatory mechanisms that control KCC2 expression in axotomized and regenerating motoneurons are unknown. Previous studies in the spinal cord point to microglia and BDNF-TrkB signaling as responsible for KCC2 downregulation in dorsal horn interneurons after peripheral nerve injury. However, blocking microglia activation specifically in the ventral horn and deleting BDNF-TrkB signaling both genetically and pharmacologically did not prevent KCC2 downregulation in motoneurons axotomized after similar nerve injuries. Moreover, we found that KCC2 expression recovers only after motoneurons re-innervate peripheral muscle. Preliminary data using RNA-scope indicates that KCC2 disappearance in axotomized motoneurons is likely controlled at the mRNA level. Therefore, we conclude that the mechanisms that control KCC2 in motoneurons after nerve injuries are quite distinct from those previously reported in the dorsal horn.

24. A *length principle* for motoneuron excitability

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Neuronal excitability is related to structural features of the axonal initial segment (AIS). Recent studies show that following manipulation of activity levels, neurons become more excitable when the AIS is longer and closer to the soma and less excitable when it moves further away from the soma. This form of activity-dependent plasticity is suggested to be a mechanism that fines tunes neuronal excitability during development. We considered the possibility that this mechanism might lead to differentiation of excitability of type S vs F motoneurons (MNs). Here we describe results of the first examination of AIS in predominantly fast vs slow motor pools in adult rats. We injected retrograde tracers in two rat muscles selected for their innervation by a pool of S (soleus) and F (medial gastrocnemius - MG) MNs. Spinal cord sections containing MNs populations from both muscles were incubated with antibodies recognizing Ankyrin-G (Ank-G), a membrane scaffold protein present at the AIS, and the voltage-gated sodium channel isoform 1.6 (NaV1.6). The average location of the AIS in the soleus MNs was 40% closer to the cell body and its length 15% longer than the AIS of MG MNs. Changes in NaV1.6 location paralleled those observed with Ank-G. This parameter emerges, therefore, as yet another property distinguishing the excitability, and possibly the recruitment sequence of motor pools and MN types.

25. Force steadiness for the dorsiflexors of the less-affected leg does not differ between individuals diagnosed with multiple sclerosis and healthy control subjects

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Due to the prevalence of problems with the dorsiflexor muscles in individuals diagnosed with multiple sclerosis (MS), the purpose of our study was to compare muscle strength, force steadiness, and motor unit discharge characteristics of the dorsiflexor muscles in individuals with MS and healthy age- and sex-matched control subjects. We expected to find that the individuals with MS would exhibit worse performance on all three outcomes than the Control group. In this ongoing study, eight subjects in each group have completed the protocol to date (MS: 49 ± 10 yrs; Control: 48 ± 11 yrs). The evaluations comprised of maximal voluntary contractions (MVC) of the dorsiflexor muscles as well as surface, high-density electromyography recordings over the tibialis anterior during isometric force steadiness tasks at 10% and 20% maximum (30 s contractions) on the less-affected leg in the MS subjects and on the dominant leg of the Control subjects. There was no statistically significant difference between groups for dorsiflexor muscle strength (MS: 12.8 ± 4.4 N•m; Control: 16.0 ± 6.6 N•m; $P > 0.05$) or for the coefficient of variation in force during the steady isometric contractions at 10% (MS: 2.3 ± 1.7%; Control: 1.7 ± 0.7%; $P > 0.05$) or 20% (MS: 2.5 ± 2.7%; Control: 1.6 ± 0.6%; $P > 0.05$) of MVC force. However, the mean interspike interval (ISI) for motor units in tibialis anterior were longer during the steady contractions for the MS subjects at both 10% (MS: 110 ± 20 ms; Control: 87 ± 15 ms) and 20% (MS: 102 ± 21 ms; Control: 76 ± 15 ms; $P > 0.05$). In contrast, the difference for the coefficient of variation for ISI was not statistically significant at 10% (MS: 26.3 ± 8.6%; Control: 26.9 ± 5.2%) or 20% (MS: 26.2 ± 5.1%; Control: 26.7 ± 4.7; $P > 0.05$). Given the absence of difference in force steadiness, there was also no statistically significant difference in the estimated variance in the common synaptic input to the motor neurons innervating tibialis anterior during the steady isometric contractions. These findings indicate that there are minimal changes in the neuromuscular properties of the less-affected leg of individuals with MS who are ambulatory.

26. Alterations in motor unit firing rates in patients with chronic inflammatory demyelinating polyneuropathy

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, or non-hereditary, chronic demyelinating neuropathy. Diagnosis is based on cerebral spinal fluid protein changes, clinical presentation and electrophysiological findings. Nerve conduction studies show multi-focal demyelination and cerebrospinal fluid (CSF) protein content is elevated with a normal CSF leukocyte count. Although these clinical features and diagnostic tests are straightforward, the classical presentations are frequently absent particularly in the acute relapsing phase of patients with CIDP. Increased understanding of the functional limitations and pathophysiology of CIDP are of particular interest due to the treatable nature of the disease. We compared dorsiflexion strength and motor unit firing rates of the tibialis anterior (TA) of CIDP (n=10) with age (64 ±15) and sex matched controls (n=10). Intramuscular EMG recordings were obtained with custom-made insulated tungsten microelectrodes (125 µm in diameter and 4.5–7 cm in length). Benefits of this technique are the ability to manipulate the electrode during a variety of contraction intensities, thereby sampling from many discrete MUs from each subject. Motor units were recorded at 25, 50, 75, 100% MVC during several brief non-fatiguing (~5s) isometric contractions. Over the series of contractions, the indwelling

electrodes were repositioned or reinserted into different portions of the muscle to achieve a representative sample. CIDP patients were ~50% weaker than controls despite equal and near maximal voluntary activation (~98%) of the dorsiflexors. Motor units collected at 75 and 100% MVC in CIDP patients had rates that were ~30 and ~50% slower, compared to controls, respectively. In contrast, MUs collected at 25 and 50% MVC had ~30% higher firing rates than controls. From these preliminary results, CIDP patients with less dorsiflexion strength have abnormalities in rate coding across a range of contractile intensities which may have concurrent implications on recruitment strategies and overall motor control.

27. Origin of acute chemotherapy-induced spontaneous activity

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Pain, dysesthesias, cramps, fasciculations, and spasms are among the principle dose-limiting side effects afflicting nearly all cancer survivors treated with platinum-based chemotherapy. This constellation of symptoms known as chemotherapy-induced peripheral neuropathy (CIPN) diminishes quality of life and limits functional capacity. Acute CIPN is consistently attributed to spontaneous motor and sensory activity. Although the evidence is largely indirect, spontaneous activity is believed to originate at ectopic sites in the peripheral nervous system outside the normal action potential initiation zones. *In-vitro* studies of motor, sensory, and dorsal root ganglia provide evidence for an ectopic location of origin for spontaneous firing. Unfortunately, these experimental models have failed to accurately reproduce the necessary circumstances to probe the mechanistic underpinnings of spontaneous firing. Methodological limitations that influence excitability independent of chemotherapy (e.g. transection of the cervical spinal cord and ventral root) reduce external validity. Therefore, the goal of this study was to determine the origins of spontaneous firing induced by platinum-based chemotherapy in sensory and motor neurons. Our preclinical model in rats enabled *in vivo* implementation of electrophysiological techniques capable of localizing the origin of spontaneously activity in intact sensory and motor neurons. To determine the origin of spontaneous motor activity, we spike trigger averaged from synchronous single-unit EMG and ventral root recordings. To determine the origin of spontaneous sensory activity, we spike trigger averaged from single Ia afferents and peripheral nerves recordings. The results were unequivocal in demonstrating that spontaneous activity originated at or near the primary sensory endings of group Ia muscle afferents and at or near the soma/initial segment of motor neurons within central nervous system. Our findings provide the first *in-vivo* demonstration of the site of spontaneous motor and sensory activity and raise further uncertainty about the involvement of ectopic firing for the treatment of acute CIPN.

28. Increased voluntary activation of the elbow flexors following a single session of chiropractic manipulation in subclinical neck pain population

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The primary aim of the study was to investigate the effects of a single session of spinal manipulation on voluntary activation of the elbow flexors in participants with subclinical neck pain using a validated interpolated twitch technique with transcranial magnetic stimulation (TMS). Eighteen volunteers with

sub-clinical neck pain participated in this study using a randomized crossover design. TMS was delivered to the motor cortex during elbow flexion contractions at 50%, 75% and 100% of maximum voluntary contraction (MVC) before and after spinal manipulation or passive neck movement (control intervention). The order of spinal manipulation and passive head movement were randomised randomized. The amplitude of the superimposed twitches evoked during different levels of voluntary contractions were recorded and analysed and voluntary activation was calculated using a regression analysis. Elbow flexion MVC increased following spinal manipulation (+2.9% ±7.4) but not passive head movement (-1.5% ±3.9). This difference between groups was statistically significant (P=0.03). The amplitude of the superimposed twitch during elbow flexion MVC was reduced following spinal manipulation (-23% ± 30, p=0.04. This results in an increased in voluntary activation of the elbow flexors (+3.2% ± 3.5, p=0.03). There was no change in the amplitude of the superimposed twitch or voluntary activation following passive head movement. Voluntary activation of the elbow flexors increased immediately after one session of spinal manipulation in participants with subclinical neck pain. A decrease in the amplitude of superimposed twitch during MVC suggests a facilitation of motor cortical output following spinal manipulation.

29. Neural motor decoders for prosthetic control

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The overarching goal of this project is to develop novel neural motor decoders for prosthetic control. As opposed to EMG decoders that measure the EMG signal from an intact but non-target muscle, the neural decoder transforms the signal measured from the severed motor axon of the target muscle into a command signal to drive the movement of a prosthetic limb. To achieve that, a multi-scale, highly-realistic computer model of the spinal motor pool was developed (Allen and Elbasiouny, 2018) to serve as a computational platform for developing and testing the new motor decoder algorithms. Two types of decoder algorithms have been developed: 1) a firing rate-based algorithm, and 2) a Kalman filter-based algorithm. Both decoders transform the aggregate discharge of the motor pool into a command signal to control the simulated prosthetic MuJoCo hand under real-time conditions. In their operation, the firing-rate based algorithm was developed based on the cellular neurophysiology of how motoneurons are activated by synaptic inputs to generate action potentials, whereas the Kalman filter-based algorithm captured the correlation between pool firing and synaptic input. Our results show that both types of neural motor decoders are fast (i.e., decoding time < the DARPA requirement of 10 ms), reliable (i.e., with accurate output in response to inputs of varying waveform, magnitude, and speed), and robust (i.e., with accurate output in response to varying activation schemes) in controlling the prosthesis. Additionally, these decoders were successful in estimating, in real-time, the input signal with dynamic changes in magnitude and rate of activation. Taken together, these neural motor decoders provide a very promising alternate option with more physiological control of the prosthesis than EMG decoders.

30. Chronic defects in repetitive firing of MNs result from a decrease in persistent inward current after chemotherapy

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For years after chronic chemotherapy, Oxaliplatin (OX) causes many debilitating peripheral effects including sensory ataxia and paresthesia. Previous in vivo studies (Bullinger et al 2011, Vincent et al 2015) of rats, weeks after a full treatment course of OX, show that muscle spindle afferents have lost

the ability to encode sustained muscle stretch. These findings are consistent with a decrease in Persistent Inward Currents (PICs), and they encouraged us to investigate, for the first time, if this deficit extends to a neuron in the CNS. We hypothesized that chronic OX causes deficits in the repetitive firing of motoneurons (MNs) due to a decrease in PICs. MN firing was measured in terminal experiments on adult F344-Pirc (model of colon cancer) rats anesthetized with isoflurane, following OX treatment. Repetitive firing was elicited during 5 second, square pulse current injections. In response, MN's fired erratically and included pauses of up to 1 second, decreasing force production of the motor unit significantly. Using computer simulations, decreasing the ratio of Na PIC to K conductances reproduced defective MN firing. Using dynamic clamp, in vivo, control MNs showed similar deficits in repetitive firing when decreasing PIC via manipulation of Na and K conductances predicted by the simulation. In OX treated rats, repetitive MN firing was rescued when increasing PIC via dynamic clamp which in turn rescued motor unit force. Finally, an FDA approved serotonergic agonist that increases PIC was administered acutely while recording from MNs in OX rats. The increase in PIC, also rescued MN firing and motor unit force production to control levels. Collectively, these findings support our hypothesis that defective MN firing with chronic OX results from a net decrease in PIC.

31. Fatigability and motor unit behavior of the dorsiflexor muscles in people with type 2 diabetes

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Men and women with diabetes mellitus and diabetic polyneuropathy are more fatigable for the dorsiflexor muscles during isometric fatiguing contractions, in part due to impaired motor unit properties. Whether people with type 2 diabetes mellitus (T2D) *without* diabetic polyneuropathy have greater fatigability is unknown. The aim was to determine the fatigability and motor unit behavior of the dorsiflexor muscles in people with T2D and controls. 12 people with T2D (7 men, 5 women; 65.6±5.0 years; 29.9±5.4 $kg \cdot m^{-2}$; 8,590±3,050 daily steps) were matched based on age, body mass index, and physical activity with 9 healthy controls (5 men, 4 women; 63.9±5.4 years; 26.7±3.5 $kg \cdot m^{-2}$; 9,240±3,910 daily steps). Motor unit discharge rate (DR), coefficient of variation (CV) of DR, and force of the tibialis anterior were quantified during submaximal contractions (10% and 40% of maximal voluntary isometric contraction (MVC)) before and after an intermittent, isometric fatiguing task (50% MVC for 6-s followed by 4-s rest until task failure). Motor units were decomposed from high-density surface electromyography (64-channel) collected during submaximal contractions. Time-to-task failure was 53% briefer in people with T2D compared with controls (6.2±3.6 vs. 13.3±9.2 min, P=0.019). During the 40% MVC task, people with T2D had greater CV of force (6.3±4.6 vs. 4.6±2.4%, P=0.041), higher CV of DR (26.4±10.5 vs. 23.9±11.5%, P=0.001) and higher mean DR (14.6±2.7 vs. 13.8±2.6 $pulses \cdot s^{-1}$, P<0.001) than controls before the fatiguing task. Similar differences between groups (T2D, control) were observed after the fatiguing task, and for 10% MVC task. Thus, the ankle dorsiflexor muscles of people with T2D with no signs of clinical polyneuropathy were more fatigable and had greater variability of force and motor unit DR than matched controls. A fatiguing contraction however, did not exacerbate differences between the T2D and control groups in motor unit behavior or force fluctuations.

32. Hyper-excitability of brainstem pathways in cerebral palsy

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Individuals with cerebral palsy (CP) experience impairments in the control of head and neck movements, suggesting dysfunction in brainstem circuitry. To examine if brainstem circuitry is altered in CP we compared reflexes evoked in the sternocleidomastoid (SCM) muscle by trigeminal nerve stimulation in adults with CP and age/sex-matched controls. Increasing the intensity of trigeminal nerve stimulation produced progressive increases in the long-latency suppression of ongoing SCM EMG in controls. In contrast, participants with CP showed progressively increased facilitation around the same reflex window, suggesting heightened excitability of brainstem pathways. We also examined if there was altered activation of cortico-brainstem pathways in response to pre-natal injury of cortical pathways. Motor-evoked potentials (MEPs) in the SCM that were conditioned by a prior trigeminal afferent stimulation were more facilitated in CP compared to controls, especially in ipsilateral MEPs that are likely mediated by cortico-reticulospinal pathways. In some participants with CP, but not in controls, a combined trigeminal nerve and cortical stimulation near threshold intensities produced large, long-lasting responses in both the SCM and biceps brachii muscles. We propose that the enhanced excitatory responses evoked from trigeminal and cortical inputs in CP are produced by heightened excitability of brainstem circuits, resulting in the augmented activation of reticulospinal pathways. Enhanced activation of reticulospinal pathways in response to early brain injury may provide a compensated activation of the spinal cord, or alternatively, contribute to impairments in the precise control of head and neck functions.

Poster Session E

33. Maximal motor unit discharge rate predicts the human rate of force development

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The central nervous system (CNS) controls muscle force by recruitment and rate coding of motor units. Maximal rate of force development thus depends on these two mechanisms. However, it has been previously argued that rate coding has a greater impact on contraction speed than recruitment (Duchateau and Baudry, 2014). In this study we directly investigated the association between maximal discharge rate of populations of motor units and rate of force development. Eighteen men (age 22.4 ± 2.0 years) performed isometric ankle dorsi-flexion contractions at maximal speed and force. The discharge timings of motor units of the tibialis anterior muscle were identified by high-density surface EMG decomposition. The rate of force development was computed and correlated to the average of the maximal motor unit discharge rates (DR_{MAX}). The rate of force development and the DR_{MAX} were computed during three phases of the contraction (0-50, 50-100 and 100-150 ms, respectively). The discharge rate was found on average to be maximum in the first 50 ms of contraction (69.28 ± 24.52 vs 49.80 ± 22.71 pps, 50 vs 100 ms time windows, respectively, $p<0.001$). The maximal rate of torque development across subjects was 481 ± 114 ($MVC \cdot s^{-1}$) and was maximum at ~90 ms following the onset of the contraction. The DR_{MAX} in the first 50 ms of contraction predicted both the absolute and normalized maximal rate of force development ($R^2 = 0.81$ and 0.84, $p<0.001$). Conversely, the DR_{MAX} in the time windows 50-100 and 100-150 were not correlated with the rate of force development. The present results demonstrate that maximal motor unit discharge rate in the very early phase of an explosive isometric contraction is the main determinant of human maximal rate of force development.

34. Transitory decrease in force of unfused tetanic contractions of motor units at a sudden reduction in stimulation frequency in rat medial gastrocnemius

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The effects of decreasing rate of stimuli for the force production and relaxation process of motor units (MUs) still are not fully understood. It is known that at linearly decreasing stimulation frequency the force decrease is slower than expected when comparing to the constant stimulation frequency. Therefore, recently observed surprising transitory force decrease during the unfused tetanic contractions in three types of motor units at sudden decrease in stimulation frequency was analyzed. 32 slow (S), 48 fast fatigable (FF) and 82 fast resistant (FR) MUs were isolated in adult female rats under pentobarbital anesthesia. Studied MUs were stimulated with several trains of stimuli composed of three phases: first, 500 ms at low frequency, second, 300 ms at high frequency and third, 500 ms at the same low frequency. The tested low frequencies for fast MUs were 10, 20, 30, 40 and 50 Hz, and high frequencies amounted to 75, 90 and 150 Hz, whereas for slow MUs low frequencies were 10, 12.5, 15, 17.5, 20 and 25 Hz and high frequencies amounted to 30, 40 and 50 Hz. For 78 of 161 studied MUs within the third phase of tetanus at the second low frequency of stimulation, a transitory force decrease to a level lower than expected for this frequency was observed. This phenomenon was approximately twice as frequent for FR (65.9%) than for FF and S MUs (27.1% and 35.5%, respectively). Moreover, the amplitude of the force decrease, when present, was the strongest for FR units (up to 36.5%) for middle-fused tetani (the fusion index 0.50–0.95). The phenomenon most probably has biomechanical background and is conditioned by distribution of contracting muscle fibers in a deep part of muscle and slow adaptation of stretched collagen fibers to the lower force level of contracting muscle fibers at reduced stimulation frequency.

35. Electrical nerve stimulation frequency and pulse duration influence motor unit discharge characteristics of the elbow flexors

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The purpose of our study was to compare the influence of five types of electrical nerve stimulation on the discharge characteristics of motor units in the contralateral biceps brachii muscle during a voluntary contraction. The electrical stimulation protocols comprised different combinations of pulse duration (0.2 and 1 ms), stimulus frequency (50 and 90 Hz), and stimulus current (greater or less than motor threshold). The electrical nerve stimulation protocols were applied to the right elbow flexors of 13 participants (26 ± 3 yrs) while they performed voluntary contractions with the left elbow flexors to match a target force set at 10% of maximum. All five types of electrical nerve stimulation increased the absolute amplitude of the electromyographic (EMG) signal recorded from the left biceps brachii with high-density electrodes. Both high-frequency conditions (90 Hz, 0.2 ms and 1 ms) reduced the standard deviation of the barycenter displacements during the voluntary contraction. The narrow-pulse, high-frequency condition (0.2 ms, 90 Hz) decreased the force fluctuations during the steady contraction being performed by the left elbow flexors after the stimulation ended, whereas the other high-frequency condition (1.0 ms, 90 Hz) increased the average force exerted by the left elbow flexors. In contrast, both low-frequency conditions (0.2 ms, 50 Hz and <motor threshold, 50 Hz) increased the duration of the mean interspike interval of motor unit action potentials after the stimulation had terminated. These findings indicate that the central effects of electrical nerve stimulation can be influenced by both stimulus pulse duration and stimulus frequency.

36. Low-cost, non-invasive, single motor unit electrophysiology in the undergraduate teaching laboratory

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Effective teaching of neuromuscular physiology to undergraduates must involve a description of how the motor unit (MU) converts motor neuron action potentials into muscle force to produce behavior. Experiential, immersive laboratory activities can enhance the learning of this phenomenon. However, even in well-equipped research laboratories, invasive recordings of single MU behavior are technically demanding. Teaching labs are thus often limited to the surface electromyogram (EMG) as the relevant electrophysiological example, with little chance to observe single cell behavior. The purpose of this presentation is to present the recording of both ensemble and single MU electrophysiology with extraordinarily simple equipment.

We developed an inexpensive, portable system capable of measuring both surface EMG and single MU action potentials. We record surface EMG with two brass brads glued to wooden sticks and an aluminum foil ground (<$0.25). The signals are led to the ~$100 gain-adjustable, battery-powered amplifier (Backyard Brains, Inc.) with alligator clips and speaker wire. A free smartphone app (Spike Recorder) displays the signals and a <$20 speaker provides audio of the EMG. The system very readily provides excellent recordings of surface interference EMG. Importantly, the handheld electrodes allow rapid and unlimited adjustment of electrode position on one muscle or to many different muscles in a session. The system has allowed us to develop a hands-on experiment called “The Hunt for a Motor Unit”. We can, with remarkable success rates, find single MU’s with reasonable signal-to-noise ratio. Students can observe recruitment, rate modulation, and de-recruitment of their own single MU. Students can also easily observe the recruitment of additional motor units and modulation of the EMG signal during different behaviors, such as chewing, pinching, smiling, and nostril flaring. We have used these demonstrations to improve our undergraduate teaching labs and community outreach programs.

37. Motor unit contribution to decreased force steadiness following active lengthening

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Activation reduction (AR), characterized by a decrease in electromyographic (EMG) activity, is a phenomenon of residual force enhancement (RFE) arising from a greater relative contribution of passive force to overall force in isometric submaximal contractions that follow active-lengthening. Although alterations in motor unit (MU) activity are thought to contribute to AR, there is a gap in understanding the cause of AR. Our study evaluated the underlying contribution of MU properties in the tibialis anterior (TA) to AR and tested for an influence on torque steadiness (TS). We hypothesized that MU discharge rates (DRs) would be lower during AR than a purely isometric contraction, contributing to less TS. Ten males (26±4years) performed 10 and 20% isometric maximum voluntary contractions (MVCs) following an active-lengthening contraction over a 30° ankle excursion, which ended at the same muscle length as a reference isometric contraction. Indwelling EMG sampled TA MU action potential trains to determine MUDR and DR variability (DRV). Triceps surae and TA surface EMG was recorded to evaluate AR and co-activation. TS was quantified as the coefficient of variation (CV) of torque. There was a ~34% AR ($p<0.05$) for the isometric contraction following active-lengthening compared with purely isometric, with no difference in antagonist coactivation ($p>0.05$). Torque CV was ~22% greater during AR at 10% and 20% MVC ($p<0.05$). Overall, the number of MUs detected was ~42% greater in the purely isometric condition than AR. In the purely isometric contractions at 10% and 20% MVC there were 51 and 47 MUs recorded, respectively with only 27 and 30 of these units quantified in both isometric and AR conditions. MUDR decreased by ~23% ($p<0.05$)

during AR compared with the isometric contraction. DRV did not differ between isometric and AR ($p>0.05$). Our findings indicate that AR can be attributed to fewer detectable MUs and reduced MUDR, which likely leads to a reduction in TS during AR.

38. Characterizing neural control of precision and power grip tasks using motor unit coherence

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There is increasing evidence that both corticospinal and reticulospinal motor pathways contribute to the control of hand muscles in humans and that the relative extent of this contribution may differ during tasks that require precise vs. gross control. For example, recent findings using transcranial magnetic stimulation over the hand representation of the primary motor cortex showed that corticospinal excitability and intracortical inhibition decreased to a larger extent during power grip (gross motor control) than during index finger abduction and precision grip (fine motor control; Tazoe and Perez, 2017). Here, we aim to characterize the neural drive across these hand motor tasks using motor unit coherence analysis.

We asked uninjured subjects (n=2) to perform index finger abduction, precision grip, and power grip while maintaining 10% of maximal voluntary contraction with the right first dorsal interosseous (FDI) muscle. High-density surface electromyography (EMG) was obtained from a 64-channel grid placed on the FDI, and real-time visual feedback of rectified, smoothed EMG from a central channel of the grid was provided during each trial. High-density EMG was decomposed into motor unit spike trains using an established algorithm (Negro et al., 2016). Composite spike trains containing the discharge of multiple simultaneously firing motor units were used to calculate motor unit coherence, which was compared among the three tasks by summing the coherence within four different frequency bins: common drive (1 – 2 Hz), alpha (5 – 12 Hz), beta (15 – 30 Hz), and gamma (30 – 60 Hz).

We found that motor unit coherence in the beta and gamma bands decreased by ~50% during power grip compared with index abduction and precision grip. Because coherence in these higher frequency bands is thought to reflect motor cortical/corticospinal influences, our preliminary findings suggest a decreased contribution from these structures during gross compared with fine hand motor tasks, consistent with previous results (Tazoe and Perez, 2017).

39. Influence of dendritic PIC location on force production in model soleus motor unit

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Persistent inward current (PIC)-generating $Ca_V1.3$ channels in motoneuron dendrites are thought to be actively recruited during normal behaviors. However, whether and how the location of PIC channels influences the force output of the motor unit remains elusive. Here, a physiologically realistic model of slow motor unit was systematically analyzed under triangular current injection at the soma of the motoneuron during isometric contraction at the optimal muscle length. The simulations of model motor unit demonstrate that: 1) the current input-force output gain on the ascending stimulation phase is not correlated with the location of PIC channels over the motoneuron dendrites, 2) the extent of force potentiation by the PIC activation on the ascending stimulation phase is not significantly influenced by the variation in the PIC channel location, and 3) the range of current intensity for self-sustained force production on the descending stimulation phase is almost constant when the PIC channels are located over the dendritic regions (≤ 600 μm) proximal to the soma of the motoneuron but then rapidly

increases as the path length from the soma increases. These results suggest that the location of PIC channels in the motoneuron dendrites might not be a crucial factor for gain modulation and force potentiation of the motor unit at the optimal muscle length.

40. UBC-Nepal expedition: Ascent to high-altitude increases motor unit discharge rates but does not affect torque steadiness of the elbow flexors

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Ascent to high-altitude (HA) represents a unique multifactorial challenge to the human body. Sequelae such as impaired cognition and neuromuscular propagation, increased sympathetic activity, and lower than normoxic partial pressure of arterial oxygen may impact motor function, but data are scant. Thus, this study aimed to measure motor unit discharge rates (MUDR) and torque steadiness (TS) in seven Lowlanders under normoxic (N) and hypoxic conditions. Data were collected 7-14 days after gradual ascent to 5050m and six months later at 344m. During 30s contractions at 10% of maximal voluntary contraction (MVC) torque, surface and intramuscular electromyographic signals were recorded from biceps brachii. TS was assessed with 3 sets of 10s contractions performed at 5, 10, 25, and 50% MVC torque and quantified as the coefficient of variation of the torque trace. MVC torque (86.5±11.0 vs. 84.1±10.4 Nm) and maximal M-wave amplitude (25.3±7.3 vs. 22.6±6.7 mV) were not different in N and HA, respectively ($P<0.69$). Mean MUDR at 10% MVC torque was lower in N (13.9±1.4 Hz) than HA (15.4±2.1 Hz; $P<0.01$). TS was not different ($P=0.16$) between conditions (for N and HA; 5%: 1.3±0.3 vs. 1.0±0.2%; 10%: 0.9±0.3 vs. 0.8±0.4%; 25%: 1.0±0.4 vs. 0.8±0.4%; 50%: 1.4±0.5 vs. 1.5±0.4%). In both N and HA, contractions at 10% and 25% were steadier than 5% and 50% MVC torque ($P<0.05$). Compared to N, acclimatization to HA led to increased MUDR for a low-intensity contraction. The documented impairment of calcium release and sequestration kinetics as well as a tendency for decreased neuromuscular propagation at HA may explain higher MUDR for the same relative target torque. Despite increased MUDRs, extended exposure to HA had no effect on TS. This preservation of motor control would be beneficial in those activities (e.g. climbing, mountaineering) where fine regulation of output is critical for performance.

41. Can we observe any signs of motor unit discharges in electroencephalography?

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The aim of this study was to investigate whether single motor unit discharges can be detected in electroencephalography (EEG) recordings. In this study, we recorded single motor unit potentials using intramuscular bipolar wire electrodes inserted into a hand muscle (Abductor Pollicis Brevis; APB) and a facial muscle (Temporalis). In addition, we recorded EEG from the masticatory motor cortex area. During the experimental sessions, subjects were asked to either contract the muscle slightly or to relax the muscle as much as possible. We have then recorded single motor units either activated by conscious effort or fired simultaneously at rest. By using this approach, we aimed to differentiate between the reflection of motor units that fired as a result of a drive coming from the motor cortex with that of motor units that fired without any conscious effort, on the EEG recording. We analyzed our data by spike-triggered averaging (STA), for which we used the single motor unit discharges as the trigger and the EEG recording as the source. Among all 45 APB units obtained from 10 subjects, regardless of their activation either with or without conscious effort, none of them displayed significant activity on the ipsilateral or contralateral motor cortex area. We did, however, observe deflections in the recordings from some of the EEG electrodes that occurred at the same latency as the trigger in 3 of these 45 APB units. In 16 of 27 temporalis units we observed large surface representations of single motor units on

the EEG electrode that was placed directly on the source motor unit. We suggest that these representations of single motor units on the EEG were caused by cross-talk, since they occurred at the same time as the trigger. Therefore, we eliminated the possibility that motor unit discharges could be traced back to the motor cortex even when it is consciously involved in firing of a motor unit.

42. The effect of moderate-duration passive muscle stretching on persistent inward currents estimated through paired motor unit analysis

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It is well established that prolonged passive stretch reduces maximal muscle force production and neural drive to the muscle. The origin of this neural inhibition is still unknown; however, some evidence suggests that passive stretch might cause prolonged inhibition of Ia afferents, which could consequently affect the ability to develop persistent inward currents (PICs) in spinal motoneurons. In humans, PIC amplitude can be estimated by calculating the delta f (ΔF). The ΔF is calculated as the change in firing rates of a lower-threshold control motor unit during the recruitment and derecruitment of a higher-threshold test unit, and is proposed to be proportional to PIC amplitude. Therefore, the aim of this preliminary study was to compare ΔFs before and after passive stretching.

Five healthy males performed isometric trapezoidal plantar flexor contractions to 20% of maximal force. Four contractions interspaced by 25 s were performed before (Control 1) and after (Control 2) 3 min of rest (Control) and immediately after three 1-min plantar flexor stretches (Stretch). Surface electromyography (EMG) was recorded from a 32-channel electrode matrix over medial gastrocnemius (MG). EMG signals were decomposed into single motor unit discharges. ΔFs were calculated for pairs of motor units that fit the following criteria: 1) rate-rate correlations ≥ 0.7; 2) test unit recruited at least 2 s after control unit; 3) control unit did not present saturation of discharge rates.

After exclusions, 23, 27 and 17 pairs of motor units at Control 1, Control 2 and Stretch, respectively, were analyzed. ΔFs were on average 4.5 (95% CI, 3.8 to 5) during Control 1, 4.7 (95% CI 3.9 to 5.4) during Control 2 and 4.3 (95% CI 3.1 to 5.4) after Stretch condition. There was no difference between conditions ($p=0.78$). In conclusion, this preliminary data suggests that moderate-duration passive stretch did not affect estimates of PICs measured at MG.

43. The development of "motoRneuron", an open-source toolbox for time-domain motor unit analyses: a case-study in motor unit synchronization methods

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Motor unit (MU) synchronization has been theorized as a control strategy for force generation through common inputs to motor neurons. Time-domain synchronization indices are calculated from peaks in cross-correlation histograms between MU discharge trains; however, there are many different methods for detecting these peaks, resulting in differing index calculations. There is currently no standard methodology or publicly available software which implements the varying methods. We developed an open-source toolbox for the freely available R programming language. The toolbox, named "motoRneuron", provides functions calculating synchronization for different methods found in the literature. Our objective was two-fold: 1) detail the program's functionality and 2) compare synchronization indices using different methods in a case-study format. The program's primary function, "mu_synch" performs a cross-correlation analysis on two MU discharge trains and analyzes the resulting histogram for peaks. Significant peaks were determined separately by the cumulative sum (cumsum) method (Keen, 2012), z-score method (DeFreitas, 2013), and subjectively by visual inspection of the cumulative sum graph (Nordstrom, 1992). Additionally, "order" and "bin-width"

arguments allow the user to define the number of recurrence intervals and histogram bin-size, respectively. A sample MU pair extracted from the forearm during an isometric contraction was used to calculate synchronization indices CIS, k', S, E, and SI. In this case study, the results (Table 1.) indicate a low degree of synchronization between the sample MU's, regardless of method. However, there is a varying degree of synchronization between methods. For example, the widely used k', which represents the ratio of synchronized discharges to expected discharges, shows a 113% difference between the visual and cumsum methods. This singular example demonstrates how a lack of consensus in MU synchronization methodologies may lead to substantially differing results between studies. The motoRneuron toolbox provides researchers with a standard interface and software to examine time-domain MU synchronization.

	Z-score	Cusum	Visual
CIS	2.410	1.963	2.246
k'	3.595	1.172	4.211
S	0.096	0.078	0.105
E	0.235	0.191	0.256
SI	0.236	0.192	0.257

Table 1. Synchronization indices calculated from motor units of the forearm using 3 different methods.

Poster Session F

44. Sub-populations of spinal V3 interneurons from layered pre-motor microcircuits

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The laminar structure of the nervous system provides flexibility in information processing. Local layered organisation provides the substrate for various inputs to be received and processed to ensure that local microcircuits generate appropriate output. Although local layers cannot be readily visualized in the spinal cord, it has been postulated that such a layered organization provides the flexibility needed for movements. To determine if local layered processing is present in the ventral spinal cord, we examined connectivity of excitatory V3 INs, a population previously shown to project to MNs, and to be involved in the stability of locomotor activities. As modelling studies have suggested that rhythm-generating circuits are not last order, we postulated that there would be both direct (monosynaptic) and indirect (oligosynaptic) V3-MN connectivity. To study synaptic connectivity patterns of ventral V3 INs, we used holographic photo-activation of caged MNI-glutamate (using a Phasor spatial light modulator system) over pre-synaptic somas while whole-cell patch clamp recordings were made in V3 INs (tdTomato) or MNs in 300 um thick slices from the lumbar spinal cord of $Sim1^{Cre/+;Rosafloxstop26TdTOM}$ mice. This allowed us to define local connectivity patterns that involved two distinct ventral V3 IN populations - ventral V3 medial ($V3_{vmed}$) and ventral V3 lateral ($V3_{vlat}$) INs and ipsilateral MNs. These local synapses followed a rule of layered connectivity in that $V3_{vmed}$ INs synapse on $V3_{vlat}$ INs that in turn have bi-directional mixed synapses with ipsilateral MNs. Thus, ventral V3 INs form distinct subpopulations that form local layers, leading to microcircuits that may be capable of the logic needed for flexible motor control.

45. **Human quadriceps motoneurons are inhibited by group III/IV afferent feedback but when tested during ongoing descending drive the responsiveness of the motoneuron pool is increased**

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Fatigue-related afferent feedback from quadriceps and hamstrings muscles reduces voluntary motor output, however its effects on motoneuron excitability are unclear. Here we examined quadriceps motoneuron excitability, with and without ongoing descending drive, during periods of post-exercise muscle ischaemia. With ischaemia, high levels of group III/IV afferent feedback are expected. Thoracic motor evoked potentials (TMEP) were assessed after a 3-min fatiguing knee extension (*study 1*) or knee flexion (*study 2*) contraction in 12 participants. Each study had two days; with or without ischaemia. Ischaemia was produced by an inflatable thigh cuff which occluded blood flow for a 2 min period post-exercise. TMEPs recorded from vastus medialis (VM) were elicited during knee extensor contractions of 25% of maximal electromyographic activity (EMG). TMEPs were additionally evoked during the EMG silent period that follows transcranial magnetic stimulation (TMS) over the motor cortex (TMS-TMEP). In the 2 minutes following the 3-min knee extension contraction (*study 1*), TMS-TMEPs were smaller during ischemia than without ischemia by 13.2% [-22.2 – -4.22] (mean [95%CI]) of baseline TMS-TMEP; P=0.025). Conversely, TMEPs elicited during ongoing descending drive were larger with ischaemia by 21% [4.9 – 38.2] (P=0.009). Similarly, after the knee flexion contraction (*study 2*), TMS-TMEPs evoked during ischaemia were 14% [-28.8 – -0.3] smaller than without ischaemia (P=0.045), whereas TMEPs were 17% [4.3 – 29.8] larger (P=0.011). Effort and pain ratings were higher during ischaemia in both studies (P<0.001). The reduction in TMS-TMEP, tested during pauses in descending drive, indicates that quadriceps motoneurons were inhibited by group III/IV muscle afferents from either the knee extensors or flexors. The higher effort with maintained feedback suggests additional voluntary drive was required to compensate for the inhibitory feedback to the motoneurons. Unexpectedly, when tested during ongoing descending drive, TMEP size increased. This suggests that group III/IV feedback acts differentially across the motoneuron pool.

46. Re-investigation on the nature and sign of transcranial magnetic stimulation-induced cortical silent period

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The objective of this study was to construct peristimulus time histogram (PSTH) and peristimulus frequencygram (PSF) using single motor unit recordings to reinvestigate the transcranial magnetic stimulation (TMS)-induced cortical silent period (CSP) in a lower limb muscle. Single pulse TMS via a double cone coil over the tibialis anterior (TA) motor area during weak isometric dorsiflexion of the foot was used in fourteen subjects. Several hundred stimuli were delivered at a frequency of about 0.3Hz and the intensity set at active motor threshold. TA electromyography (EMG) was recorded with surface and intramuscular fine wire electrodes. Three subjects also received sham double cone coil TMS pre and post a spinal manipulation intervention. The single motor unit data were analysed from the constructed PSF and PSTH. From the averaged surface EMG data motor evoked potentials (MEPs) and CSPs were constructed and analysed. Twenty-eight single motor units were identified. Using a combination of probability and frequency-based analysis techniques, the silent period observed following threshold and suprathreshold TMS during a weak contraction of the human tibialis anterior were characterised. Our results demonstrate that the CSP can be divided into two parts, with the first

part being excitatory due to the falling phase of the EPSP generated by MEP (and hence is a continuation of an excitatory response). Recordings from single motor units provided evidence that during the first half of CSP motor units displayed higher discharge rates than the mean prestimulus discharge rate. Therefore, this period of CSP needs to be defined as excitatory but not inhibitory. The second part of the CSP reflects a genuine inhibition caused not by the cortical involvement but by a tendon organ activation as the result of the MEP induced muscle contraction. Tendon organ activation by the MEP generates this late CSP inhibition (secondary response due to MEP induced contraction).

47. Development of a dual-conditional transgenic mouse model for genetic targeting of Renshaw cells in adult animals

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Renshaw cells (RCs) are interneurons that inhibit motoneurons (MNs) and receive direct input from recurrent collaterals of motor axons as they exit the spinal cord. This recurrent circuit is the oldest inhibitory circuit known in the mammalian CNS, but it is unclear what functions it mediates during motor behavior. Known connections of RCs—MNs and Ia inhibitory interneurons (IaINs)—suggest several roles, including limitation and decorrelation of MN firing, focusing Ia activation to specific motor pools, regulating motor input-output gains, and adjusting joint stabilization and co-contraction through actions on IaINs; however, these roles are yet to be validated—despite extensive research on RCs—due to the difficulty of isolating RC activity from other network elements. Recent advancements on the genetic fingerprint of RCs opened possibilities for genetic targeting. We focused on calcium-buffering protein genes: *calb1, calb2* and *pvalb.* We used mice carrying a trimethoprim (TMP) inducible *dgCre* variant controlled by the *calb1* promoter to genetically label RCs. Single TMP injections at selected post-natal days labeled 99% of RCs at P21 and 88% at P60, with significant off-target labeling predominating in the dorsal horn. We then vetted *calb2* (calretinin) and *pvalb* (parvalbumin) as candidates to further restrict targeting to RCs and found that both are expressed in approximately 60% of genetically labeled RCs at P21. An intersectional approach by crossing *calb1-dgCre* with *pvalb-flp* mice and injection of TMP at P10 labeled 53% of RCs at P21 and 25% of RCs at P60 with dramatic reductions in off-target labeling. Non-RC labeled spinal interneurons were scattered primarily throughout the dorsal horn (0.4 cells per RC), with very few in the ventral horn (0.02 per RC). Additional genetic labeling was detected in cerebellar, superior olive and reticular thalamic interneurons. These results constitute the first genetic targeting of adult RCs to bypass development.

48. Adapting sensory and motor inputs generate non-adapting motor output

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Synaptic inputs from multiple peripheral and central sources carrying different information get integrated in the final pathway to movement via spinal motoneurons. Depending on the synaptic strength and firing frequency of the presynaptic neuron, these inputs exhibit different patterns of short-term plasticity (either facilitation or depression) though the motor output of the spinal cord is maintained steady during most motor tasks.

To investigate how varying sensorimotor inputs could generate a steady motor output, we studied the interaction between two inputs to motoneurons in the adult mouse spinal cord in vitro. The inputs were induced by a short train of electrical stimuli delivered either to the dorsal roots (sensory input), the descending axons of the vestibulospinal tract (Motor input), or both of them simultaneously (Sensorimotor inputs). Stimulation was delivered at different frequencies, intensities, and neuromodulatory states. The motor output in response to stimulation was recorded from single

motoneurons (excitatory postsynaptic potentials, EPSPs) using intracellular sharp electrodes, and from the ventral roots (compound action potentials, coAPs) using extracellular wire electrodes.

Our results show that at physiological frequencies (25 and 50 Hz), the sensory input exhibited short-term depression, while the motor input exhibited short-term facilitation however their simultaneous stimulation generated a steady motor output. Interestingly, when EPSPs' amplitudes were compared to coAPs' amplitudes during sensorimotor stimulation, EPSPs exhibited sub-linear summation whereas coAPs exhibited supralinear summation, indicating a discrepancy in inputs summation between the cellular and pool levels. Computer simulations suggested that this discrepancy in inputs summation at the cellular and pool levels is due to the firing threshold of motoneurons acting as a high-pass filter. This prediction was confirmed experimentally when methoxamine was administered to enhance the excitability state of the spinal cord (thereby lowering the firing threshold).

The data suggest that integration of multiple, despite adapting, excitatory inputs help generate a stable motor output by maintaining the synaptic potentials above the firing threshold, which is more readily achievable at higher neuromodulatory states.

49. Re-wiring of the Renshaw circuitry using single motor units in human

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One of the first identified circuits that control the motor neuronal output using its own activity is the recurrent inhibitory circuitry of Renshaw. It is known that an activated Renshaw cell (RC) inhibits motor neuron output by shunting its excitation. Although Renshaw cell circuitry has been investigated for decades, its exact function has yet to be discovered due to the limitation of techniques to study RCs in human subjects. Therefore, the aim of this study was to use a reliable method and investigate the duration and the strength of Renshaw inhibition in humans. The findings were aided by computer simulations and motor neuron recordings. After optimizing the stimulation of the motor axons in a reproducible manner, we recorded single motor units from human subjects and analyzed the individual sets of action potentials using probability as well as frequency-based analysis. For this purpose, the largest motor axons in the tibial nerve were electrically stimulated and the smallest motor units innervating soleus muscle were recorded using intramuscular electromyography, simultaneously. A total of 54 distinct units from 12 subjects were analyzed. The duration of the inhibition was compared with the data obtained previously from rat hypoglossal motor neurons and the computer simulation of the single motor units. The frequency methods indicated that the duration of the Renshaw inhibition was between 30 to 45 ms depending on the background firing rate of units. The duration of inhibition and the background firing rate were inversely proportional. Also, probability-based methods showed that the strength of the inhibition is directly proportional to the number of motor axons stimulated. Hence, these findings propose high correlation with the controlled animal studies and that this method can be used as a reliable tool to shed more light on the functions and dysfunctions of the RC system.

50. Re-evaluation of the post-activation depression in human neuronal networks

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The monosynaptic Hoffmann Reflex (H-reflex) which is evoked using electrical stimulation of a mixed muscle nerve has been studied extensively. Specifically, the amplitude variation of this reflex has been used as a tool to investigate many neuronal networks in humans, including recurrent inhibition and

presynaptic mechanisms. One of the causes underlying the change in amplitude of the H-reflex is post-activation depression (PAD), which has been suggested to be a presynaptic phenomenon. High-frequency stimulation above 0.2 Hz, and up to 10 Hz, induces H-reflex inhibition due to PAD. In this study, we aimed to investigate PAD using various electrical stimulation rates and voluntary contraction levels. To pinpoint the characteristics of the PAD, we applied surface electromyography to the soleus muscle. Using various interstimulus intervals (i.e. 1, 2, 5, 10 and 15 seconds), stimulus intensities and muscle contractions levels (i.e. 0%, 5%, 10%, 25% and 35% of maximum voluntary contraction) the reflex response was assessed in 10 healthy subjects. Our study confirms the results of previous studies regarding the effect of the interstimulus interval on the amplitude of the H-reflex. We also show that PAD can be reduced in strength at any stimulation rates as long as the level of voluntary contraction is above 25% of maximum voluntary contraction. These findings suggest that motor cortex output is one of the most responsible elements in the attenuation of PAD. Putting all the current findings together, we propose a novel hypothesis in which the circuitry responsible for PAD involves plateau potentials of interneuronal networks.

51. Exploring the use of patterned sensory stimulation to augment spinal reflex excitability

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The Hoffmann (H-) reflex is often used to examine Group Ia transmission onto alpha motoneurons to provide insight about pre- and post-synaptic mechanisms responsible for acute and chronic neuroplasticity. Patterned stimulation of sensory afferents from antagonist muscles has been used to induce plasticity in H-reflex amplitude arising from alterations in Group Ia reciprocal inhibition. When assessed transiently with a condition-test pulse paradigm, stimulating cutaneous afferents innervating the foot reduces Group Ia presynaptic inhibition of soleus motoneurons and therefore facilitates H-reflex amplitudes. Conditioning effects of long lasting patterned sensory stimulation to cutaneous afferents innervating the foot (that mimic repeated ground contact loading) has yet to be examined. As a first step, we examined how 20 minutes of patterned and alternating stimulation between the feet affects spinal reflex excitability. Stimulus trains (550ms; consisting of 28x1ms pulses at 50Hz, 1.2 x radiating threshold) were applied simultaneously to the sural and distal tibial nerves at the ankle every second during conditioning. Prior to and following the conditioning stimulation, we evoked soleus H-reflexes and muscle compound action potentials (M-waves). H-reflex and M-wave recruitment curves were recorded at rest, during brief (~90s) arm cycling and with sural conditioning (train of 5x1ms pulses at 2xRT with a C-T = 80ms). Preliminary data indicate a general increase in H-reflex excitability following patterned sensory stimulation. Transient sural conditioning was less effective following patterned sensory stimulation, indicating that the increased excitability of the H-reflex is likely attributable to a reduction in presynaptic inhibition of soleus Group Ia afferents.

52. Neuroinflammation and the permanent removal of Ia afferent synaptic inputs on axotomized motoneurons

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Information regarding limb position is transmitted through Ia afferents and is integrated into spinal circuit networks to modulate motor output in response to environmental perturbations. However, following peripheral nerve injuries a neuroinflammatory response occurs in the ventral horn that coincides with Ia afferent synapse degradation. The final outcome after nerve regeneration is completed depends on the type of injury; nerve transection causes permanent loss of Ia synapses and

the reflex, while both recover after nerve crush. Our goal was to find causal relationships between spinal neuroinflamation and Ia synaptic losses. We further hypothesized that modulation of neuroinflammation properties could adjust synaptic plasticity to various levels according to injury severity. To test these hypotheses, we performed different types of nerve injuries in transgenic mouse models that allowed us to study resident microglia activation (CX3CR1-GFP mice) and infiltration of peripheral CCR2-expressing macrophages (CCR2-RFP mice), combined with various global and cell-specific knockout models to investigate signaling pathways that triggered the immune response and their relation to Ia synapse loss. Deletion of colony stimulating factor 1 (CSF1) release from specifically axotomized motoneurons (MNs) prevented microglia activation. Moreover, sciatic nerve transection results in long lasting microglia activation and differentiation towards CCL2-relasing pro-inflammatory phenotypes. This did not occur after sciatic nerve crush. Only after differentiation of pro-inflammatory phenotypes there was infiltration of CD45/CCR2 cells, including T-cells, monocytes and dendritic cells. CCL2-CCR2 signaling was especially critical for monocyte infiltration, some of which appear to transform into microglia-like cells by morphology and genetic lineage labeling. Lack of these cells in CCR2 global KOs correlated with better preservation of ventral horn Ia synapses. In conclusion, promoting CCR2+ monocyte infiltration amplifies Ia synapse losses. Moreover, the properties of spinal neuroinflammation after different nerve injuries is under fine control by signaling between axotomized MNs, microglia and penetrating blood-derived CCR2+ immune cells.

53. Motoneuronal and cortical excitability as well as central fatigue during and after a sustained submaximal elbow extensor task

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Compared to other muscle groups (e.g., elbow flexors, knee extensors or dorsiflexors), few studies have investigated muscle fatigue of the elbow extensors (EE). Although data are limited, it appears that the EE respond uniquely to fatigue and, thus, warrant further study. Therefore, the purpose of this experiment was to investigate motoneuronal and cortical excitability as well as central fatigue in EE during and after a submaximal task. Seven participants (4 females) performed a 15min sustained isometric EE contraction at the level of electromyographic activity (EMG) recorded at 15% MVC torque, followed by recovery contractions over 5min. Evoked potentials were recorded from triceps brachii in response to transcranial magnetic stimulation (TMS; motor evoked potentials, MEPs), cervicomedullary stimulation (cervicomedullary motor evoked potentials, CMEPs) and brachial plexus stimulation (maximal M-wave; Mmax). MEPs and CMEPs were elicited with or without a conditioning TMS pulse 100ms prior to the test stimulus. To calculate VA pre- and post-fatigue, superimposed (SIT) and resting tetani (RT) were evoked via trains of 5 stimuli (100Hz) delivered over triceps brachii. Mmax area did not change with fatigue, whereas the unconditioned CMEP was reduced ~10% and the unconditioned MEP was increased by ~50% compared to control values. The conditioned CMEP and MEP were both reduced by ~40%. During recovery, there were negligible changes to the unconditioned responses and the conditioned CMEP. Conversely, the conditioned MEP showed some degree of recovery (~20% below control). VA decreased from 96% prior to fatigue to 83% at task termination, and showed incomplete recovery (90% at 5min). Changes to motoneuronal and cortical excitability during fatigue and VA after fatigue mimic adaptations observed previously in the elbow flexors. However, unlike other muscle groups, the EE show a persistent depression and enhancement of motoneuronal and cortical excitability, respectively.

Poster Session G

54. Neurotransmitters segregation within spinal recurrent circuitry

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Early studies at the neuromuscular junction established the role of acetylcholine as the main transmitter mediating muscle contraction, through its release from motoneurons' terminals. However, motoneurons' axons also make synaptic contacts onto Renshaw cells as well as other motoneurons. It is now established that Renshaw cells are excited through a mixed cholinergic-glutamatergic synapse. However, the two transmitters systems appear to be segregated, either at the pre- or post-synaptic level, since, while unitary currents evoked through paired recordings between motoneurons and Renshaw cells are invariably mixed in both neonatal and adult animals, miniature synaptic events, resulting from the release of a single vesicle, are never mixed. Segregation is even more extreme for synapses between motoneurons, that are, surprisingly, purely glutamatergic, at the single synapse as well as population level and at any developmental stage. Motoneurons therefore differentiate their transmission system according to their post-synaptic target. We also show that there is a high degree of convergence between motoneurons, both within and across adjacent segments, with each cell receiving inputs from at least 5-10 other motoneurons. Importantly, putative Fast type motoneurons receive greater recurrent excitation that Slow type ones. We therefore suggest that recurrent excitation might constitute an important and previously neglected mechanism of amplification of the motor output.

55. The functional role of activity-dependent plasticity in motoneurons during development revealed by metabotropic glutamate receptor activation

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Abstract withdrawn.

56. Cholinergic-mediated coordination of rhythmic sympathetic and motor activities in the newborn rat spinal cord

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In the present study, we investigated intrinsic spinal cord mechanisms underlying the physiological requirement for autonomic and somatic motor system coupling. Using an *in vitro* spinal cord preparation from newborn rat, we demonstrate that the specific activation of muscarinic cholinergic receptors (with oxotremorine) triggers a slow burst rhythm in thoracic spinal segments, thereby revealing a rhythmogenic capability in this cord region. Whereas axial motoneurons (MNs) were rhythmically activated during both locomotor activity and oxotremorine-induced bursting, intermediolateral sympathetic preganglionic neurons (IML SPNs) exhibited rhythmicity solely in the presence of oxotremorine. This somato-sympathetic synaptic drive shared by MNs and IML SPNs could both merge with, and modulate, the locomotor synaptic drive produced by the lumbar motor networks. This study thus sheds new light on the coupling between somatic and sympathetic systems and suggests that an intraspinal network that may be conditionally activated under propriospinal cholinergic control constitutes at least part of the synchronizing mechanism.

57. TRPM5 is required for thermosensitive plateau potentials in lumbar motoneurons

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The majority of neonatal spinal motoneurons display thermosensitive plateau potentials which emerge at temperatures > 30°C (Bouhadfane et al., 2013). These bistable behaviors are, to a large extent, determined by the interplay between three currents: L-type I_{Ca}, I_{NaP}, and I_{CaN}; but the identity of the channels underlying this "ménage à trois" is uncertain. We previously showed that the thermosensitivity relies on I_{CaN} mainly carried by Na^+. By means of genetic and pharmacological approaches in neonatal rats and mice, we here investigated which "thermoTRP" channel(s) mediates I_{CaN} in lumbar motoneurons. The genetic deletion or pharmacological blockade of TRPV1-3 and TRPM4 channels did not alter the slow afterdepolarisation (sADP) responsible for the plateau potential evoked by a brief excitation. Instead, sADP is enhanced or decreased by the respective pharmacological activation or blockade of TRPM5 channels. Likewise, the pharmacological blockade of TRPM5 channels reversibly prevents plateau potentials. All together, these data show a significant contribution of TRPM5 channels in generating sADP to promote plateau potentials. Because plateau potentials are thought to be important in postural functions, TRPM5 channels may have a behavioural role in modulating the postural control.

58. The role of group II metabotropic glutamate receptors in the lumbar spinal cord

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The participation of metabotropic glutamate receptors of group II (2 and 3 subtypes) in the synaptic activity modulation was studied in spinal neurons of lampreys, turtles and rats. It was shown that mGluR 2/3 appear to be mostly located presynaptically in mammalian spinal cord where they mediate presynaptic inhibition of glutamate release and therefore function as negative feedback controller of excitatory transmission. Presynaptic mechanism of modulation of mIPSPs by mGlu II receptors in the turtle spinal motoneurons was revealed. For lower tetrapods little is known about the role of mGluR 2/3. We have used a combination of extracellular and intracellular recordings of the frog spinal motoneuron activity with application of mGluR 2/3 ligands and fluorescence immunohistochemistry to examine relationships between distribution and function for mGluR2/3 in the frog spinal cord.

It was shown that the application of DCG-IV (0.05-5 μM) decreased the short latency amplitude of ventral root potentials evoked by dorsal root stimulations up to 63%. The number of action potentials in the DR-PSP was reduced to 70% and the response area was reduced to 30% during agonist [1 μM] application, which may also indicate the presynaptic involvement of mGluR2/3 in the synaptic transmission of motoneurons and interneurons. The frequency of miniature synaptic activity of motoneurons (mPSPs) with application of 1 μM DCG-IV was suppressed from 6% to 70%, on average by 32%, without considerable changing amplitude. The frequency of the inhibitory fraction of miniature postsynaptic potentials (mIPSPs) was decreased by 18% without decreasing the average amplitude. DCG-IV application in the higher concentrations (2 - 4 μM), resulted in a considerable increase in frequency and amplitude of sPSPs and production of action potentials in some motoneurons. It was revealed that application of DCG-IV influenced on the RMP, amplitudes of antidromic APs and their afterpotentials. So, the postsynaptic action of mGluR 2/3 agonist was seen. The amplitude of AHPs was changed as during the.application of serotonin. According to the literature data, a 5-HT 2A R - mGluR 2 complex is formed in the brain of mammals. The fluorescence immunohistochemistry of mGluR II distribution in frog lumbar spinal cord has revealed the mGluR 2 –ir of motoneurons. The ventral commissural interneurons have no mGluR 2 –ir signals. mGluR 3-ir was seen in the myelin envelopes of injured sites of the roots, nerves and white matter fibers. Our results demonstrate a

possible complex role for mGluR II subtypes participation in modulation processes of vertebrate network output.

59. Size-dependent differences in mitochondrial density & morphology of phrenic motor neurons

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Neuromotor control of diaphragm motor units is dependent on the orderly recruitment of motor neurons (MNs) in a size-dependent manner. Type S and FR motor units comprise smaller, more easily recruited MNs that innervate fatigue resistant type I and type IIa muscle fibers. Type FInt and FF motor units, comprise larger, rarely recruited MNs innervating more fatigable type IIx and IIb muscle fibers. The activity and energy demand upon MNs of S and FR motor units is greater than that of MNs from type FInt and FF, due to the high duty cycle (~40%) of breathing, which would cause marked fatigue in FInt and FF motor units. This energy demand in both MNs and motor unit muscle fibers is met by mitochondria. To preserve homeostasis, mitochondrial functions are regulated by dynamic, continuous cycles of fusion and fragmentation. We hypothesized that mitochondrial density and mitochondrial fusion will be greater in smaller phrenic MNs that are more frequently active during ventilation.

In six adult Fischer 344 rats, phrenic MNs were retrogradely labeled by intrapleural injection of Alexa488-conjugated CTB. Three days later, cervical transdural infusion of MitoTracker Red (Invitrogen) was performed every 10m for 1.5 h under anesthesia (xylene/ketamine). Following euthanasia by exsanguination, 4% paraformaldehyde perfused spinal cords were removed, processed, horizontally sectioned on a cryostat at 50 µm and mounted onto slides. Two-channel sequential confocal z-stack (0.50 µm step size) mosaics of phrenic MNs and mitochondria were acquired using a 63x oil immersion objective (1.4 NA, 1200x1200 pixel density, Olympus FV1000) and analyzed using Elements software (Nikon). The surface areas of phrenic MNs were measured and divided into tertiles. The lower tertile of phrenic MNs had greater mitochondrial volume densities, greater mitochondrial aspect ratios and form factors and greater mean individual mitochondrial volumes than upper tertile MNs. Our results suggest that MNs of S and FR motor units have increased mitochondrial density, supporting their high energy demand to sustain ventilation. Their increased mitochondrial fusion may underlie their resilience to MN loss in aging and disease.

60. Lanthionine ketamine derivatives induce autophagy in motoneurons

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Autophagy is a cellular digestion process that contributes to cellular homeostasis and adaptation by the elimination of proteins and damaged organelles. Impaired autophagy has been implicated in neurodegenerative diseases, including motoneuron disorders. Therefore, upregulation of autophagy is a promising therapeutic approach. Lanthionine ketimine (LK), an amino acid metabolite found in mammalian brain tissue at low concentrations, possesses potent neuroprotective, neurotrophic and anti-neuroinflammatory properties. Both LK and its cell-permeable derivative LKE, activate autophagy in rat glioma and human neuroblastoma cells. We hypothesized that LKE treatment induces autophagy flux in motoneurons. Using a mouse motoneuron-like hybrid cell line (NSC-34), we tested the impact of LKE in autophagy modulation. Changes of LC3 protein and the conversion-ratio of LC3I to LC3II (the gold standard for measuring autophagy), were obtained by Western blot. For fluorescence visualization of the autophagy flux, mCherry-GFP-LC3 plasmid was transfected in NSC-34 cells. This fluorescent reporter allows monitoring LC3 flux because the GFP signal is sensitive to the acidic and/or proteolytic

conditions of the lysosome lumen, whereas mCherry fluorescence persists under these environments. Results showed that LKE induces autophagy as reflected by an increase in both LC3I and LC3II protein. Confocal microscopy images showed that motoneurons treated with LK derivatives display increased mCherry puncta (lysosomes) compared to yellow puncta (autophagosomes) indicating an induction in autophagy flux. In conclusion, LK derivatives constitute a promising treatment option to induce autophagy flux in motoneurons, which may serve to mitigate motoneuron degeneration and loss, and preserve motor function in motoneuron disease.

61. Dendritic distribution of Cav1.3 and SK channels in spinal motoneurons: a simulation study

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Retrovirus (RV) infection of the central nervous system in humans and animals is associated with a broad spectrum of cognitive and motor abnormalities. Moreover, human endogenous retroviral (HERV) expression has been implicated as playing a causative role in several sporadic neurodegenerative diseases including multiple sclerosis, amyotrophic lateral sclerosis, and schizophrenia. To understand how RVs mediate neurodegeneration, we have undertaken a comprehensive neurophysiological interrogation of rapid, stereotypic, murine leukemia virus (MLV)-induced motor neuron disease models characterized by progressive non-inflammatory spongiform neuropathology. Our initial studies on the inferior colliculus (IC) demonstrated that glial infection selectively altered neurons characterized by after hyperpolarization firing (rebound neurons; RNs). These interneurons lost rebound firing, became hyperexcitable, and disrupted rhythmic circuits and auditory brainstem responses. Notably, similar but milder changes were observed with a control “non-neurovirulent” RV. To assess glial-mediated motor neuron (MN) changes, we extended these investigations to the vestibular nucleus (VN), a classical motor area in the brainstem. The virus-induced MN alterations observed in the VN included elevated firing thresholds, decreased firing frequencies, large inhibitory post-synaptic potentials (IPSPs), and depolarization block with ramp stimulation that failed to recover on ramp decrease. Importantly, “non-neurovirulent” virus caused similar, but milder MN changes, including threshold elevation, decreased firing frequency at maximum ramp stimulation and depolarization block at very high current ramps (however, with recovery during ramp decrease). These findings establish clear neurophysiological hallmarks for how RV expression within CNS glia can alter the intrinsic properties of MNs, RNs and their associated circuits. Moreover, these findings provide important mechanistic insight into virus-induced clinical manifestations and set the stage for addressing whether similar neuron/circuit alterations are induced by human RVs or HERVs. We discuss the nature of the specific glial targets involved, and the means by which they precipitate the observed neurophysiological changes.

62. Retrovirus-induced spongiform neurodegeneration is physiologically characterized by glial-mediated motor neuron depolarization block

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While it has been a half century since the discovery of large C-bouton synapses on spinal motoneurons (Mn), and a decade since their role in motor output was demonstrated, the mechanisms by which these modulatory synapses regulate Mn firing are not clear. Anatomical studies have revealed post-synaptic clusters of proteins such as calcium-activated (SK2 and SK3) and voltage-activated (Kv2.1) potassium channels, yet we know little about how these channels are modulated by acetylcholine release at the

pre-synaptic terminal. Physiological knowledge of the interactions between pre and postsynaptic components of the C bouton is fundamental to our understanding of how the nervous system produces appropriate motor outputs for a given task. Here, we study the role of Kv2.1 channels in the production of Mn spike trains in the lumbar (P10-16) and cervical (P6-8) spinal cord. Using whole cell patch clamp electrophysiology, repetitive firing was stimulated and recorded in Hb9::eGFP^{+} Mns before and after bath application of 100 nM Guangxitoxin (GxTx-1E), a peptide toxin that primarily inhibits Kv2.1 channels at this concentration. Current clamp experiments show that GxTx-1E significantly broadened spike ½ width and reduced afterhyperpolarisation (AHP) amplitudes in both cervical and lumbar MNs. With these changes in action potential waveform, we observed a significant reduction in initial doublet frequency, and depolarising block was reached at lower current inputs after GxTx-1E application. However, sustained firing frequency (last 2 spikes) was unaffected by GxTx-1E. Our results suggest that Kv2.1 activation allows rapid repolarisation of Mn spikes to produce high firing frequencies in initial spike doublets and reduces depolarisation block. Experiments in both human and animal models suggest that high frequency initial spike doublets contribute to greater force, and rate of force production in muscle. Therefore, C bouton activation of Kv2.1 channels may help muscles to meet the demands of tasks requiring rapid and/or high force outputs.

63. Regulation of motoneuron firing by Kv2.1 channels in the mouse lumbar and cervical spinal cord

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While it has been a half century since the discovery of large C-bouton synapses on spinal motoneurons (Mn), and a decade since their role in motor output was demonstrated, the mechanisms by which these modulatory synapses regulate Mn firing are not clear. Anatomical studies have revealed post-synaptic clusters of proteins such as calcium-activated (SK2 and SK3) and voltage-activated (Kv2.1) potassium channels, yet we know little about how these channels are modulated by acetylcholine release at the pre-synaptic terminal. Physiological knowledge of the interactions between pre and postsynaptic components of the C bouton is fundamental to our understanding of how the nervous system produces appropriate motor outputs for a given task. Here, we study the role of Kv2.1 channels in the production of Mn spike trains in the lumbar (P10-16) and cervical (P6-8) spinal cord. Using whole cell patch clamp electrophysiology, repetitive firing was stimulated and recorded in Hb9::eGFP^{+} Mns before and after bath application of 100 nM Guangxitoxin (GxTx-1E), a peptide toxin that primarily inhibits Kv2.1 channels at this concentration. Current clamp experiments show that GxTx-1E significantly broadened spike ½ width and reduced afterhyperpolarisation (AHP) amplitudes in both cervical and lumbar MNs. With these changes in action potential waveform, we observed a significant reduction in initial doublet frequency, and depolarising block was reached at lower current inputs after GxTx-1E application. However, sustained firing frequency (last 2 spikes) was unaffected by GxTx-1E. Our results suggest that Kv2.1 activation allows rapid repolarisation of Mn spikes to produce high firing frequencies in initial spike doublets and reduces depolarisation block. Experiments in both human and animal models suggest that high frequency initial spike doublets contribute to greater force, and rate of force production in muscle. Therefore, C bouton activation of Kv2.1 channels may help muscles to meet the demands of tasks requiring rapid and/or high force outputs.

64. Time invariance in SCA6 relates to altered neural activation and exacerbated functional deficit

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Spinocerebellar ataxia type 6 (SCA6) is a genetic disease causing cerebellar degeneration with significant motor control impairments. Our purpose was to characterize motor control in SCA6 during isolated contractions and determine its association with brain activity, muscle activity, and functional capacity. Twenty-two individuals diagnosed with SCA6 (60.4 ± 8.8 yrs., 15 F) and 8 healthy controls (55.3 ± 9.7 yrs., 4 F) performed 50 submaximal ballistic goal directed contractions (15% maximum at 180 ms) with ankle dorsiflexion. We quantified the following: 1) Motor control - dysmetria and endpoint variability in force and time during ankle dorsiflexion; 2) Brain activity - using resting functional connectivity and free-water diffusion magnetic resonance imaging analyses; 3) Agonist muscle activity – TA EMG burst and burst variability during ankle dorsiflexion; 4) Functional capacity - using the International Cooperative Ataxia Rating Scale (ICARS), the Scale for the assessment and Rating of Ataxia (SARA), and a manual dexterity test. We identified two distinct groups of SCA6 patients based on time endpoint variability. The first group (n=12) exhibited low time variability (<15%; time invariant group). The second group (n=10) exhibited time variability comparable to healthy controls (>20%; time variant group). The time invariant SCA6 group exhibited impaired functional capacity as evidenced from greater scores in ICARS ($P<0.05$) and SARA ($P<0.05$), and lower scores in the manual dexterity test ($P<0.05$). Time variability was predicted by the TA EMG burst duration variability ($R^2=0.67$; $P<0.05$) and activity of the cerebellum ($R^2=0.86$; $P<0.05$). Our findings provide novel evidence that there is a distinct subtype of SCA6 characterized by invariance in time endpoint. This group of SCA6 exhibit impaired functional capacity, and differential activation of the brain and muscle.

Poster Session H

65. On the identification of plantar flexor's fasciculation potentials from US imaging and multichannel sEMG

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Muscle fasciculations, resulting from the spontaneous activation of motor neurons, may be associated with neurological disorders. Despite its clinical relevance, current means do not seem to accurately reveal the presence of fasciculations. While intramuscular electromyograms (EMGs) have been shown to be too selective, ultrasound (US) images may lead to the identification of muscle movements not associated with fasciculation potentials. Conciliating US images and surface EMGs sampled from multiple muscle regions may therefore provide a sensitive and specific approach to identifying muscle fasciculation. Here we assess this issue for the ankle plantar flexors while a single, healthy subject was lying in prone position. Surface EMGs were collected with an array of 32 electrodes (1cm Inter-Electrode Distance, IED), spanning the whole, posterior aspect of the leg. US images were acquired concurrently with EMGs, with the US probe positioned alongside the electrode array. Monopolar (MONO) and differential EMGs, obtained for 1 (SD1) and 3 (SD3) cm IEDs, were considered to assess the effect of electrode selectivity on the identification of fasciculations. Preliminary results indicate 2.8, 1.5 and 1.0 fasciculations/s were respectively identified for MONO, SD3 and SD1 EMGs. These numbers decreased to 2.0, 0.8 and 0.5 fasciculations/s when considering EMGs sampled in correspondence of the location of the US probe, which provided 0.5 fasciculations/s. Although the number of fasciculations identified by US approached that identified from SD1 recordings, the rate of agreement between the two techniques was lower than 13% for all cases. Although preliminary, these

results suggest EMGs and US provide complementary information on the identification of fasciculations: surface EMGs are sensitive to fasciculations taking place with short intervals and in different, proximo-distal muscle regions whereas US are sensitive to fasciculations occurring deeply within the muscle tissue. The integration EMG-US seems therefore a promising approach to increase the detection sensitivity to muscle fasciculations.

66. Relocation of the axonal initial segment in lumbar motoneurons of rats receiving chemotherapy

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Preliminary findings from our lab (see poster Nardelli et. al.) show that chronic treatment with Oxaliplatin (C-OX) disrupts repetitive firing of motoneurons (MNs), i.e. C-OX significantly *reduces* MN excitability. Other preliminary findings from our lab (see poster Housley et. al.) show that acute OX treatment (A-OX) significantly increase spontaneous activity of MN i.e. A-OX *increases* MN excitability. We hypothesize that the chronic hypo-excitability reflects a compensatory mechanism. Among possible mechanisms, we considered change in the MN axon initial segment (AIS). Recent studies have shown that increased neural activity can displace the AIS away from the soma and reduce neuron excitability. These observations led us to evaluate AIS location in MNs of C-OX rats. Spinal cord sections from C-OX and untreated controls were incubated with an antibody that recognized Ankyrin-G (Ank-G), a membrane scaffold protein present mainly at the AIS, and the voltage-gated sodium channel isoform 1.6 (NaV1.6). The average AIS distance from the soma was 52% longer in C-OX than in untreated controls. AIS length showed no significant difference among groups. NaV1.6 relocated together with Ank-G. These findings are consistent with a compensatory response to hyper-excitability in A-OX rats, whereby AIS shifts away from the MN soma to reduce excitability.

67. The central nervous system modulates the neuromechanical delay in a broad range for the control of muscle force

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Force is generated by muscle units according to the neural activation sent by motor neurons. The motor unit is therefore the interface between the neural coding of movement and the musculotendinous system. Here we propose a method to accurately measure the latency between an estimate of the neural drive to muscles and force. Further, we systematically investigate this latency, that we refer to as the neuromechanical delay, as a function of rate of force generation. In two experimental sessions, nine subjects performed isometric finger abduction and ankle dorsiflexion sinusoidal contractions at three frequencies and amplitudes [0.5, 1, 1.5 (Hz) and 1, 5, 10 % of the maximal force (%MVC)], with a mean force level of 10% MVC. The discharge timings of motor units of the first dorsal interosseous and tibialis anterior muscle were identified during these contractions by high-density surface EMG decomposition. The neural drive sent to muscles was estimated as the cumulative discharge timings of the identified motor units. The estimated neural drive predicted 80 ± 0.4 % of the force fluctuations and consistently anticipated the force output by (average across muscles and conditions) 194.6 ± 55 ms. The neuromechanical delay decreased non-linearly with the rate of force generation (R^2 = 0.82 ± 0.07; exponential fitting) with a broad range of values (from 70 ms to 385 ms) and was shorter for the first dorsal interosseous (164.5 ± 60 ms) than for the tibialis anterior muscle (224.7 ± 50 ms). In conclusion, we provided a method to estimate for the first time the delay between neural control and force

generation and we showed that this delay is muscle-dependent and is modulated within a wide range by the central nervous system.

68. Activation of knee extensor muscles during rapid torque development in young and old men and women

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Adequacy of activation during rapid voluntary contractions is more limited in old compared to young adults and can be shown by comparing the voluntary and electrically-evoked rate of torque development (RTD). However, it is unknown whether the activation of rapid voluntary contractions during knee extension differs between men and women, and whether the sex differences persist in old adults. The purpose of this study was to compare the maximal RTD of young and old men and women during electrically-evoked isometric contractions and rapid voluntary contractions with the knee extensors. Twenty young (20-32 years; 10 women) and 20 old adults (71-93 years; 10 women) performed sets of single (200-μs duration, 120 – 660 mA) and double pulse (100 Hz inter-stimulus interval) stimulations of the femoral nerve at supramaximal intensities followed by rapid voluntary isometric knee extensions at target torques that were matched to electrically-evoked torques (10%-40% maximal torque). Surface electromyography (EMG) was recorded from the vastus lateralis muscle. The key findings were: 1) The ability to rapidly generate isometric knee extension torque was ~36% lower during voluntary contractions compared with electrically-evoked contractions, and this difference increased with age (44%); 2) Old women had ~15% lower RTD than the old men, with minimal sex differences in the young adults during voluntary contractions; 3) The peak rate of rise in the rectified and smoothed EMG was greater in young than old adults, and was associated with the maximal voluntary RTD for young adults (R^2=0.32, P=0.03) but not old adults (R^2=0.13, P>0.05); and 4) The maximal voluntary RTD was more variable in the old compared to young adults, and the old women compared with old men. Thus, the lower and more variable knee extensor RTD with aging during voluntary contractions was likely due to deficits in neural activation because there were minimal age differences in the electrically-evoked RTD. Furthermore, these age differences in RTD and variability were larger in old women than old men.

69. Coordination of orofacial musculature for speech and sound production

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Understanding the neural control and coordination of speech musculature during the production of spoken language has been an enduring challenge for scientists and clinicians alike. There is a widespread assumption that the nervous system manipulates a limited set of ‘muscle synergies’ or ‘motor modules’ to produce speech.

However, there is no consensus on the number or composition of synergies, their flexibility once established, or their dependence on linguistic context or complexity.

In this study, we utilize a comprehensive battery of EMG analysis techniques to determine the type of neural connectivity that exists among bilateral muscles of the lip, larynx, jaw, and nose during production of isolated speech sounds, words, or connected speech. Overall coordination among muscles is assessed using pairwise correlations and principle component analysis of surface EMG signals, motor modules are characterized using non-negative matrix factorization, and neural connectivity is determined by assessing regular and partial EMG coherence, which characterizes the strength and frequency spectrum of neural drive shared among muscles. We then apply the same comprehensive battery of techniques to compare unemotional speech with

'emotionally-expressive speech', where orofacial muscles are called upon to multi-task and to incorporate vocal or non-vocal emotional content into the normal speech production task. Finally, we assess whether the patterns of muscle coordination observed above are measurably different in adults with Parkinson's disease, where loss of vocal tone modulation and facial expressiveness are among the earliest and most common symptoms.

We show the neural coordination among orofacial muscles is more a function of the particular physical requirements for sound production than of linguistic context or meaning. Remarkably, when an emotional component is added to the speech production task, the typical patterns of muscle coordination are disrupted, with shared neural drive among muscles affected most. Last, individuals with Parkinson's disease exhibit much higher levels of shared drive across muscle pairs than age-matched peers.

70. Corticospinal excitability to the biceps brachii during arm cycling at various power outputs

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The influence of motor output intensity on corticospinal excitability has primarily been assessed during tonic contractions, with limited work having been done during rhythmic, locomotor outputs. The primary objective of this study was to examine corticospinal excitability to an upper-limb muscle over a wide range of arm cycling intensities (i.e., power outputs). Corticospinal and spinal motoneurone excitability were assessed using transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES), respectively. TMS-induced motor evoked potentials (MEPs) and TMES-induced cervicomedullary-evoked potentials (CMEPs) were recorded from the biceps brachii during the mid-elbow flexion phase of arm cycling at 6 different power outputs (i.e., 25, 50, 100, 150, 200 and 250W). A secondary, methodological, objective was to examine the influence of stimulation intensity on MEPs and CMEPs during the various arm cycling power outputs. Thus, MEP and CMEP amplitudes were matched to 10 and 40% M_{max}. Preliminary data analysis shows that significant increases in MEP and CMEP amplitudes ($p<0.001$ for both) occurred as arm cycling power output increased, suggesting that enhanced spinal motoneurone excitability could partially account for the overall increase in corticospinal excitability. Interestingly, however, as the power output of arm cycling increased, the gain in MEP amplitude (i.e., slope) was 2.7x higher than that of the CMEPs at the low stimulation intensity (i.e., 10% M_{max}; $p=0.001$) and 1.2x higher using the higher stimulation intensity (i.e., 40% M_{max}; $p=0.5$). Physiologically, this suggests that increases at the supraspinal level, not spinal motoneurones, are predominantly responsible for the overall increase in corticospinal excitability as cycling intensity increases. Methodologically it is noted that the higher stimulation intensity resulted in a plateau of the MEP amplitude at ~100 W while CMEPs were still increasing.

71. High-density electrodes for intramuscular electromyographic recordings

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We present the development of a high-density intramuscular sensor that comprises 40 detection sites arranged on the bottom and top layers of a thin film structure of polyimide. The polyimide substrate is composed by three 5-μm layers deposited on top of each other with platinum and gold sputtered in

between to form the electrode contacts and the tracks, respectively. The contacts are opened in the bottom and top layers of the polyimide by reactive ion etching. The resulting detection sites are oval (140 μm x 40 μm) and spaced 0.5 mm apart.

The electrode was used to record intramuscular multichannel signals from the tibialis anterior muscle of a healthy individual during steady and ramp contractions in the range 10-30% of the force recorded during maximal voluntary contraction (MVC). The resulting signals were decomposed with a modified version of the Convolution Kernel Compensation Algorithm (Holobar & Zazula, 2007), specifically designed for the intramuscular high-density recordings. The signal quality was assessed calculating the peak-to-peak amplitude of the motor unit action potentials resulting from the decomposition and the root mean square of the baseline noise. Twenty-seven motor units were identified from a 10-s steady contraction at 10% MVC. The mean amplitude of the detected motor unit action potentials was 1.1±0.7 mV while the baseline noise was 40±17 μV across all channels. Thirty-eight motor units were identified from a ramp contraction at 30% MVC. The average discharge rates of the motor units in the 2-s plateau were correlated to the respective recruitment thresholds, showing an inverse relation between the two variables (R2=0.49). The new electrode enables a high-density sampling of the intramuscular electrical activity with high signal-to-noise ratio. The increased number of detection sites with respect to the first multichannel electrode we introduced (which had 16 detection sites, Muceli et al. 2015) allows automatic accurate decomposition of a higher number of motor units.

72. Closed-loop control of afferented muscles determines the amplitude of force variability and its power spectrum

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Accurate and precise movement executions are confronted with variability associated with generation of muscle force. Such variability arises from various sources including mechanical properties of muscles and limbs, motor unit properties, proprioceptive feedback, and descending neural commands. Previously, contributions of individual sources have been studied in isolation and in a feedforward manner. However, those factors interact during closed-loop control, which describes nearly all experimental paradigms in which muscle force must be voluntarily controlled. Recently, we showed using a closed-loop simulation of an afferented muscle that neuromechanical interactions among neural noise, mechanical properties of musculotendon unit, proprioceptive feedback and error corrective mechanism suffice to explain cardinal features of involuntary force variability previously observed experimentally. Here, we attempt to extend this observation by incorporating new elements in our model. New elements added to our existing model include stochastic motor unit firing patterns, conversion of neural firing into muscle force, and additional spinal feedback pathways within and across muscles (pathway involved with monosynaptic Ia excitatory feedback, Ia inhibitory interneurons, Ib interneurons, Renshaw inhibitory interneurons, propriospinal interneurons,). Our results show that motor unit properties are important, yet are typically insufficient to explain the majority of force variability or its frequency spectrum. Importantly, we demonstrate previously an unrecognized influence of coordinated activities between two muscles on the amplitude and spectral features of force variability. These results highlight potential importance of such neuromechanical interactions in understanding the generation of force variability in precise and accurate motor tasks and explaining physiological mechanisms of altered neuromuscular control in health and diseases.

73. Changes in neuromuscular propagation during intermittent maximal voluntary contractions: a separate analysis of the M-wave phases

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An exercise-induced decrease in the peak-to-peak amplitude of the compound muscle action potential (M-wave) is usually interpreted as impaired neuromuscular propagation. However, we have recently shown that the amplitude of the M-wave first and second phases might change in a completely different manner over the course of a sustained maximal voluntary contraction. The main purpose of the present study was to examine separately the first and second phases of the M wave during 4 min of repeated intermittent 3-s maximal voluntary contractions (MVCs) in the knee extensors. Twelve healthy male participants (25 ±2 years) volunteered to participate in this study. They were asked to perform 48 successive isometric MVCs (knee angle = 90°) of 3-s duration. M waves (*vastus lateralis*, *vastus medialis* and *rectus femoris* muscles) were evoked by supramaximal single electrical stimulations of the femoral nerve delivered between each MVC. The amplitude, duration, and area of the M-wave first and second phases were measured separately, together with muscle conduction velocity, force, and temperature. During the intermittent MVCs, the amplitude of the first phase increased for ~3min (+12-16%, $p<0.05$) and stabilized thereafter, whereas the second phase initially increased for ~1min (+11-22%, $p<0.05$), but decreased subsequently. The enlargement of the first phase occurred in parallel with a decline in muscle conduction velocity. Also, a significant temporal association was found between the amplitude of the first phase and MVC force. Conversely, there was no temporal association between the second phase amplitude and muscle conduction velocity or MVC force. In conclusion, our results confirm that only the amplitude of the first phase can be used reliably to detect changes in neuromuscular propagation, while the second phase might be affected by muscle architecture.

Poster Session I

74. Mechanisms of fatigability after ischemic conditioning in men and women

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Exposure to brief periods of circulatory occlusion and reperfusion before an exercise (i.e. ischemic conditioning - IC) has been suggested to decrease exercise-induced fatigability, but the mechanisms are not known. It is also not known if IC has similar effects in the fatigability of men and women. The goal of this study was to determine the effects of IC on the time to task failure and voluntary activation of the lower extremity muscles during isometric contractions. 8 men (28 ± 5 years) and 8 women (29 ± 5 years) were submitted to cycles of ischemia and reperfusion by inflating a cuff to the non-dominant leg and arm in 3 separate and randomized sessions: A) IC that consisted of 3 cycles of ischemia and reperfusion of 5 minutes each; B) Sham session where cuffs were inflated for only 1 minute (not sufficient to induce ischemia), but reperfusion and total times of intervention were similar to those of the IC session; C) Control session with no cuffs involved. Placebo induction was performed by saying that both IC and sham would improve performance compared to control. During each session, isometric contraction of the plantar flexor muscle was performed at 20% of maximal voluntary contraction (MVC), with the dominant leg, until task failure. Voluntary activation was assessed by the twitch interpolation technique [% activation = 100 × (1 – superimposed twitch/ resting twitch)] at baseline and task failure with supramaximal doublet stimulation of the tibial nerve. At baseline voluntary activation was similar across sessions (94 ± 5%) in men and women. At task failure voluntary activation was greater for men compared with women in the IC session (87 ± 6 vs. 80 ± 6 %, respectively; session × sex: $P = 0.02$), whereas sham session had minimal effects on voluntary activation compared with control for men and women (session and session × sex: $P > 0.05$). Time to task failure was greater in the IC session for men

but not women (25.1 ± 4 vs. 17.2 ± 2 min respectively, session × sex: $P = 0.03$). Compared with control, the sham session had minimal effects on time to task failure (15.8 ± 2 vs. 16 ± 2 min respectively, session effect: $P = 0.96$) without interaction with sex ($P > 0.05$). Thus, compared with the control session, IC increased time to task failure and prevented the exercise-induced reduction in voluntary activation of the plantar flexor muscles in men but not women. Placebo effects induced in the sham session had minimal effects in these variables.

75. Organisation and reorganisation of excitable domains of motoneurone axons

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Action potentials are generated at axon initial segments and conducted along myelinated axons from one node of Ranvier (NoR) to the next. We have previously shown that the axon initial segments of spinal motoneurones are plastic and show changes in length in various disease and injury states. The goal of the current experiments was to determine whether motoneurone NoRs display similar plasticity. To first characterise the normal structural organization, we performed immunohistochemistry on ventral roots of 10 adult (110 day) male C57Bl /6J mice. To identify the nodal, paranodal (PN) and juxtaparanodal (JPN) region we used antibodies recognizing Na^+ channels, the scaffolding protein Caspr 1, and K^+ channels (Kv1.2) respectively. Measurements were made of node length, width and surface area, PN length and width and JPN width.

Our results characterized a set of rules governing the organization of the NoRs, for example, the wider the node, the shorter the PN length ($P<0.0001$). Nodal width is also a stronger determinant of overall nodal surface area than nodal length. Large diameter motor axons were also more likely to show PN and JPN border disruption ($P<0.0001$).

To explore how these parameters change with age, NoRs of aged mice (~730 days old) were analysed. In aged mice nodal length is decreased by 10% ($P<0.0001$) however the width is increased by 8% ($P=0.11909$) resulting in no overall change in surface area of the node. PNs where slightly shorter, maintaining the node width-paranode length relationship shown in the younger mice. Disruptions between PN and JPN borders, however, were 10% more frequent in the aged motor axons.

To test if the NoR of motoneurones show activity dependent plasticity, the sciatic nerve was stimulated at 100Hz for 2 hours (10 young and 8 aged mice). At 1-hour post-stimulations there was an 11.6% increase in the width of the NoR ($P=0.0401$), resulting in an overall increase in surface area of 24% ($P=0.0005$).

76. Transcutaneous nerve stimulation curtails the spinal recruitment effect of wide pulse, high frequency neuromuscular electrical stimulation

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Wide pulse, high frequency (WPHF) neuromuscular electrical stimulation (NMES) (pulse duration: 1 ms, stimulation frequency: >80 Hz) is thought to increase the reflexive activation of motor units in the spinal cord compared with conventional NMES (pulse duration: <400 µs, stimulation frequency: 15-40 Hz), possibly through activation of persistent inward currents (PICs). Another electrical stimulation paradigm, transcutaneous electrical stimulation (TENS), modulates neural processing of sensory information in the spinal cord, is also thought to affect PICs development. We evaluated the effect of TENS on the mechanical and electromyographic (EMG) responses to WPHF NMES, and hypothesized that TENS would reduce the force evoked by a bout WPHF NMES.

Eight males and two females took part in this crossover study. *Triceps surae* force and *soleus* EMG responses to a bout of WPHF NMES (3 x 20 s contractions interspersed by 40 s recovery) were assessed before (Pre) and after (Post) a 15 min period of rest (Control trial) or TENS (TENS trial). Force time integral (FTI, the area under the force trace) and sustained EMG activity (i.e. EMG activity that continues after the final WPHF NMES pulse) were quantified for each bout of WPHF NMES. The presence of sustained EMG activity is suggestive of PICs and motor units being recruited through the afferent pathway. Data are presented for the change between Pre and Post (i.e. change = Post / Pre x 100). Values are presented as median with 25^{th} percentile and 75^{th} percentile.

TENS reduced the magnitude of WPHF NMES evoked force (FTI change; Control trial: +13 (-7 and 45) %, TENS trial: -50 (-83 and -6) %, $p = 0.0098$) and sustained EMG activity (sustained EMG activity change; Control trial: +3 (-5 and 20) %, TENS trial: -9 (-40 and 4) %, $p = 0.0059$). In the TENS trial the change in WPHF NMES evoked force was strongly associated with the change in sustained EMG activity ($r_s = 0.95$, $p = 0.0001$).

Our results suggest that the force evoked by WPHF NMES is produced in part through a pathway that can be modulated by TENS. Whether PICs are implicated remains to be tested more mechanistically.

77. Axotomy and intramuscular Botox injections cause contrasting structural changes in axon initial segments of spinal motoneurones of adult rats

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The axon initial segment (AIS) is the region of most neurones that is responsible for the initiation of action potentials. Recent evidence has demonstrated that this structure can display considerable plasticity. Reductions in AIS length of cortical neurons have been observed following various forms of brain injury. Such injuries affect synaptic inputs, the soma, dendrites, axons and/or connectivity with other neurones. It therefore remains unknown whether selective damage to axons distal to the AIS induces structural changes of the AIS.

The goal of the present experiments was therefore to investigate structural changes of the AIS of axotomised rat gastrocnemius motoneurones at two-week post injury. With this method we can selectively injure the distal axons without damage to other parts of the motoneurone. Following axotomy, gastrocnemius motoneurones have been shown to exhibit excitability changes consistent with AIS plasticity.

Intramuscular injections of botulinum toxin (Botox) result in similar electrophysiological changes in gastrocnemius motoneurones, suggesting that loss of functional connectivity is enough to drive such changes. We therefore also investigated whether intramuscular Botox injections into rat gastrocnemius muscle caused similar changes to the AIS as axotomy after 2 weeks.

A combination of retrograde labelling and immunohistochemistry was used to label AISs of affected spinal motoneurones under these conditions and non-treated sides were used as internal controls. An 18.4 % reduction in AIS length was observed following axotomy ($P<0.0001$, 7 rats, control=211 cells, axotomised=169 cells), accompanied by focal distal swellings of the AIS. By contrast Botox injections resulted in a 5.1% increase in AIS length ($P<0.001$, 7 rats, control=167 cells, Botox=172 cells). Our results suggest that reductions in AIS length occur as a consequence of axonal injury whereas a functional loss of connectivity with its target results in homeostatic increases in AIS length, with neither change being observed following additional controls undergoing hindlimb immobilization.

78. Activity-induced motor axon plasticity in the median nerve of massage therapists

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Few have detailed the changes in motor axon properties in response to chronic alterations in neuromuscular activity in the absence of disease or injury. This type of data may provide important insights into mechanisms underlying activity-induced motoneuron plasticity. We have compared motor axon excitability properties of the median nerve in 8 male massage therapists and 12 untrained age-matched men. The therapists worked in a rehabilitation hospital in China for an average of 5 y (range, 3-8 y), conducting an average of 10 massages per day (20-30 min ea.) on patients, 5-6 days per week. Much of the massage work was completed by the right arm (~70% of the total massage time) and right thumb (~ 70% of right arm time), according to subject interview. Excitability properties were determined bilaterally by stimulating the nerve at the wrist and recording the compound muscle action potential (CMAP) over the abductor pollicis brevis (APB). The percentage change in stimulus threshold (i.e., the current needed to evoke a 40% CMAP) in response to various conditioning stimuli (strength-duration, threshold electrotonus, current-threshold relationship, and recovery cycle) was tracked by computer (i.e., threshold tracking). The threshold changes provide an indirect estimate of membrane biophysical properties including the resting potential and ion channel conductance. We found that mean (±SD) accommodation during 100 ms subthreshold depolarizing currents (i.e., threshold “sag”) (27.1±5.1% vs. 23.0±4.2%) and the threshold undershoot following current offset (-22.5±5.6% vs. -18.9±6.3%) were larger in the therapist’s right than left side axons (P = 0.002 and 0.01), and larger than either control side (P< 0.05). Similarly, subexcitability (i.e., reflecting the afterhyperpolarization period) was larger in the therapist’s right than left side axons (15.0±4.2% vs.13.1±3.8%, P =0.008), and larger than the controls. There were no right-left differences in excitability properties in the controls. Our findings suggest greater slow K^+ conductance in the right-side axons of the therapists, possibly due to increased ion channel expression secondary to greater thenar muscle activity.

Poster Session J

79. Neural plasticity in response to the acquisition of a visuo-motor task

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The acquisition of a visuo-motor task is accompanied by changes within the central nervous system involving spinal and supraspinal sites. To further document neural plasticity associated with motor learning process, seventeen young healthy volunteers repeated a visuo-motor task that consisted of ankle flexion-extension movements with an amplitude of 30°. An inertial load corresponding to 15% of the maximal voluntary contraction (MVC) force of the subject was attached to the foot pedal so that the plantar flexion phase requires lifting the load. The signal of the angular position of the pedal was displayed on a screen as a red dot, and the subjects had to place the red dot inside a white circle that moved vertically on the screen. The sequence of acquisition of the visuo-motor task consisted of ten blocks of 20 flexion-extension cycles. Before and after the acquisition sequence, Hoffmann (H) reflexes, motor evoked potential (MEP) from transcranial magnetic stimulation of the motor cortex were recorded in soleus and medial gastrocnemius (MG) during isometric contractions performed at 15% MVC. H reflexes were also recorded during 2 blocks of the visuo-motor task before and after the acquisition sequence. The performance in the visuo-motor task was improved after practice, especially within the plantar flexion phase. Furthermore, the H-reflex amplitude was depressed during isometric contractions (-24%) and the plantar flexion phase of the visuo-motor task (-13%), but only in MG. No significant change was observed for MEP but a correlation between changes in H-reflex and MEP was observed (r = -0.65) in MG. These first observations indicate a muscle- and phase-related modulation of sensory

inputs converging onto spinal motor neurons in response to the acquisition of a novel visuo-motor task. Motor unit recordings before and after visuo-motor task acquisition sequence are in progress to assess the effects to those adaptations on motor unit discharge characteristics.

80. Hypoxia-triggered micturition behavior: does timing matter?

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We have previously demonstrated in rats that exposure to moderate hypoxia (10-12% O_2) during bladder filling can trigger a premature micturition reflex with coordinated bladder contraction, external urethral sphincter (EUS) bursting activity, and voiding. In these experiments, the hypoxic exposure was delivered approximately midway between micturition events; thus, the relationship between the degree of bladder filling and the "hypoxia-triggered micturition" behavior is unclear. The goal of the present study was to develop a further understanding of hypoxia-triggered micturition with particular attention to the possible relationship with bladder filling. To this end, we evaluated the impact of 90 s exposure to moderate hypoxia delivered at different times during bladder filling in urethane-anesthetized, spontaneously breathing adult female Sprague Dawley rats (n=8). Saline was continuously infused into the bladder to elicit reflex micturition events, with the rate of infusion initially adjusted to achieve baseline bladder inter-contraction intervals (ICI) of ~4 min. Following baseline recording of $\geq$60 min of spontaneous reflex micturition events, the rat was exposed to an hypoxic episode initiated either early (~30% ICI) or late (~60% ICI) in bladder filling between spontaneous micturition events; 2 early and 2 late hypoxic exposures (in random order) were performed in each rat. We found that hypoxia was effective in eliciting a premature micturition event in ~70% of the early exposure trials and ~88% of the late exposure trials. These data suggest that hypoxia-triggered micturition may be independent of the degree of bladder filling; however, the CNS sites and mechanisms involved still need to be determined.

81. Cholinergic modulation of the acquisition and performance of skilled motor behaviors

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The activity of cortex is shaped by a variety of neuromodulatory inputs which influence circuit function and result in changes to cognitive and behavioral outcomes. Cortex receives widespread cholinergic innervation, and activation of these inputs results in cortical neuron desychronization, increased arousal and improved sensory discrimination. However, despite the well-documented innervation of motor cortex by ascending cholinergic projections, little is known regarding the role of cholinergic modulation in the acquisition or performance of skilled motor behavior. This work aims to ascertain the influence of cholinergic input during the learning and performance of dexterous forelimb reach in the adult mouse.

Temporally and spatially precise stimulation of basal forebrain (BF) cholinergic projection neurons was achieved using fiber optic light delivery in mice expressing channelrhodopsin in cholinergic neurons (B6.Cg-Tg(Chat-COP4*H134R/EYFP,Slc18a3)6Gfng/J) or through AAV2-driven expression in all neuronal subtypes of BF (AAV9.hSyn.hChR2(H134R)-eYFP.WPRE.hGH, Penn Viral Vector Core). Mice were trained to perform a dexterous forelimb reach to obtain a food pellet. Optical stimulation (20 Hz, 10 ms pulse duration, 500 ms) was applied following a successful dexterous reach throughout learning, or in previously trained animals.

Optical stimulation of BF cholinergic neurons during learning resulted in faster skill acquisition and enhanced final performance of a dexterous reach. ChAT-ChR2 mice receiving 0.5 mW of optical stimulation (n=3) achieved an average success percentage of 67.3±2% during the final 4 days of learning compared to implanted animals receiving 0 mW that achieved an average success percentage of 60.38±2.3% (n=13; p=0.0182). However, higher intensity stimulation (3 mW), or stimulation not

paired with a reach success both lead to disruption of the ability to learn the task. In animals previously trained to perform the reach behavior, stimulation enhanced performance above baseline (n=5; 0.3mW p= 0.0030; 0.5mW p=0.0086; 1mW p=0.0148). Finally, optical stimulation of a pan-neuronally expressing channelrhodopsin (ChR2) in BF enhanced motor performance above cholinergic stimulation alone, suggesting that other BF neuromodulatory systems may augment the effect of Ach in modulating motor behavior (0.1mW stimulation: AAV-ChR2=81.93% enhancement (n=2) vs ChAT-ChR2=23.7% enhancement (n=5); paired t-test p=0.0128).

These results demonstrate that the BF projection system modulates the motor cortex of a healthy mouse to enhance the acquisition and performance of dexterous motor tasks. The ascending cholinergic system has dose-dependent effects on motor behavior, where overstimulation of cholinergic afferents can hinder learning.

82. Temporally precise vagus nerve stimulation enhances motor learning and performance of a skilled forelimb reach task

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Vagus nerve stimulation (VNS) paired with execution of a motor behavior has been shown to increase cortical plasticity and improve rehabilitation following motor impairment. However, the influence of temporally-paired VNS on motor outcomes in healthy animals has not been fully explored. Here, we implement a novel chronic VNS mouse model to study the effects on motor learning in a healthy animal. Wildtype C57B6 mice were implanted with a flexible silicon cuff with an internal diameter of 100 µm (Cortec, MicroSling) on the left cervical vagus nerve. Following a two-week recovery, mice were trained to perform a dexterous forelimb reach to obtain a food pellet. VNS (30 Hz, 0.3mA, 100 µs pulse width) was applied immediately following a successful completion of a reach during either the learning process (n = 5) or in an animal already proficient in the task (n=5). To investigate the circuit mechanism responsible for effects of VNS on skilled motor learning, a separate cohort of mice expressing an immediate-early gene-driven(cfos) destabilized GFP (B6.Cg-Tg(Fos-tTA,Fos-EGFP*)1Mmay/J; n = 3) received VNS, and brain and brainstem tissue were collected 1 hour later. In a third experiment, alterations to cortical circuit dynamics during VNS were investigated in mice expressing a calcium indicator in motor cortex neurons (C56BL/6J-Tg(thy1-GCaMP6 GP5) imaged while freely-moving using a miniscope (UCLA Miniscope).

VNS paired with reach success increases performance throughout all phases of learning: early (days 1-4, $p<0.001$), middle (day5-9, $p<0.05$), and late (10-14, $p<.01$). In addition, paired VNS improves the performance of the dexterous reach in previously trained animals by 20% ($p<0.001$). Histological analysis of cfos expression shows neuronal activation in NTS (where vagal afferents terminate), locus coeruleus (a noradrenergic nucleus) and basal forebrain (a cholinergic nucleus), suggesting that VNS may mediate motor learning through cholinergic and/or noradrenergic means. Analysis of neuronal firing during VNS revealed decorrelated spiking in superficial motor cortex neurons. These results suggest that temporally-paired VNS can influence the learning and performance of a skilled motor task, and this effect may be mediated by alterations in motor cortex circuit dynamics due to neuromodulators.

83. Task dependent changes in motoneuron excitability in humans

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Abstract withdrawn.

84. Using neuromorphic computing to explore the interaction between the fusimotor system and descending alpha-motoneuron drive to generate simple voluntary movements

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The role of the fusimotor system during voluntary movement has been difficult to study because gamma motoneurons and muscle spindle afferents are difficult to access in humans. Therefore, we developed a neuromorphic system that implements the stretch reflex circuits of an agonist-antagonist muscle pair acting on a metacarpophalangeal joint to produce finger flexion-extension, including independent alpha- and gamma (Ia and II)-motoneuron pathways—simulating integrate-and-fire neurons in real-time on Field-Programmable Gate Arrays (FPGAs). Each muscle was driven by 256 muscle spindle afferents, 128 cortical neurons, 768 alpha-motoneurons separated into 6 motor unit subpopulations of 128 neurons with recruitment and rate coding, and 128 muscle spindles, with a delay of 32 ms in the short-latency reflex pathway and 64 ms in the long latency reflex pathway. This allows us to put our knowledge of sensorimotor circuitry to the ultimate test of physical implementation using robotic and cadaveric fingers.

Previously, we performed 3,888 ramp-and-hold joint rotations ({50,100,150,200} deg/sec) while sweeping across 9 firing rate values for each of static and dynamic fusimotor drive (0—200 pps in steps of 25 pps) and 3 firing rate values ({0,5,10}% MVC) of cortical drive, repeating each parameter set four times while keeping other model parameters constant. We obtained a detailed map of how higher dynamic fusimotor drives enhanced the phasic (ramp) force and EMG response while higher static fusimotor and cortical drives affected both phasic and tonic (hold) responses. We now extend this work to demonstrate how the amplitude and phase relationships between sinusoidal alpha- and gamma-motoneuron drive affect the amplitude and phase of free (voluntary) flexion-extension movements — resulting in both adequate and inadequate movements. Moreover, these relationships are further modulated when Golgi tendon organs and Ib interneurons are included in our neuromorphic circuits.

85. Common drive and self-sustained firing in cervical multifidis motoneurons in neck pain patients and healthy subjects

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Neck pain (NP) influences paraspinal muscle function, however the neurophysiology of this phenomenon is poorly understood. We aimed to investigate the degree of coordination of motoneuron activity in cervical multifidus (CM) in NP subjects and healthy controls (HC). Specifically, we looked for signs of self-sustained firing and rotation of activity between MUs and explored the degree of common drive to the motoneuron pool. Fine-wire electromyography (EMG) was utilised bilaterally in CM in 10 NP subjects and 15 HC. Paired recordings of simultaneously discharging MUs were used to determine cross correlation of neuronal drive represented as the common drive coefficient (CDC). Linear mixed models were employed to test the effects of a number of independent variables on CDC. Viable EMG data from 21 electrodes in 13 HC, and from 17 electrodes in 9 NP subjects showed that MUs were recruited from inactivity to tonic discharge lasting for several minutes without changes in discharge rate of other already active units, and activity was rotated between MUs. The final mixed model based on 348 unilateral and 263 bilateral MU pairs demonstrated lower CDC in bilateral vs. unilateral MU pairs (0.11; 95% CI 0.09 to 0.14; P <0.0001), and in NP vs. HC subjects (0.13; 95% CI 0.05 to 0.21; P = 0.003). CDC was also lower during sitting vs. standing (0.07; 95% CI 0.04 to 0.10; P <0.0001), and lower in voluntary vs. spontaneous activity (0.07; 95% CI 0.02 to 0.11; P = 0.004) R^2 = 0.51. Long-lasting activity within narrow firing rate ranges was rotated between MUs, which we suggest was

probably due to activation and inactivation of self-sustained discharge in individual motoneurons. Motoneurons to CM are under the influence of varying degrees of common drive depending on the postural task, and these strategies were altered in the presence of NP.

86. Doublet discharges in cervical multifidis motoneurons in neck pain patients and healthy subjects

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Motor unit (MU) doublet firing of cervical multifidus (CM) muscles has not previously been described. It has been argued that the basic features of doublet firing are *qualitatively* similar to some traits of motoneuron firing under the conditions of a plateau potential. We investigated the presence of double discharges in healthy controls (HC) and neck pain (NP) subjects. Fine-wire electromyography (EMG) electrodes were implanted bilaterally in CM in 15 HC and 10 NP subjects. We were able to discriminate 289 distinct Motor units (MU) with a total of 384 610 intervals from 21 electrodes in 13 of the HC, and 117 MU with 148 200 intervals from 17 electrodes in 9 of the NP subjects. Doublets were defined as two action potentials of the same shape and nearly the same amplitude, occurring consistently in relation to one another at an interval of 2.5–20 ms. We found at least one doublet discharge in 221 of the 289 MU recorded in HC, and in 71 of the 117 MU recorded in NP subjects. Median intra-doublet interval duration was 6.12 ms (quartiles 5.36 – 7.74 ms; n = 9448), whereas median interval duration during non-doublet activity was 123.82 ms (quartiles 106.6 – 146.5; n = 514 406). Doublets would often occur as one or a few at the start of discharge episodes, or as periods of repetitive doublet discharge lasting up to several minutes during tonic activity. The longest doublet trains were of over 5 minutes duration. In the present material we see initiation and cessation of doublet activity independently of non-doublet firing during quiet sitting and standing with no appreciable increase in effort. We argue that our results provide further evidence for the hypothesis of the plateau potential as one of possible mechanisms controlling motoneuron rhythmic firing in humans.

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