« Spinal Circuits in Motion : From Mice to Men »

A Satellite Symposium of NeuroFrance 2025

Tuesday, 13 May 2025, 13h30-17h30

Faculté des Sciences Pharmaceutiques et Biologiques
Amphithéâtre C, 15 Avenue Charles Flahault, Montpellier, France

Organized by:

CMEP - Club de la Moelle Épinière et de ses Pathologies

Under the Auspices of:

IRME - Institut pour la Recherche sur la Moelle Épinière et l'Encéphale

Registration Information:
Attendance is free but mandatory. Please confirm your participation by emailing Frédéric Brocard at frederic.brocard@univ-amu.fr by **Friday, 9 May 2025**.

Special Acknowledgment:

We extend our thanks to **Cécile Hilaire and Cédric Raoul** for their invaluable assistance in organizing this event on-site.

Program:

13:30–13:40: Welcome Address (Frédéric Brocard).

13:40–14:55: **Session 1: Spinal Mechanisms and Locomotion** (Chair: Cécile Hilaire)

- 13:40–13:55: *Serotonergic Neurons of the Caudal Raphe: Descending Connectivity and Contribution to Skilled Locomotion in Mice* (Yahia M. et al.)
- 13:55–14:10: *SK3 Channels Work in Tandem with T-type Ca^{2+} Channels to Gate Rhythmogenesis within the Central Pattern Generator for Locomotion in Mice* (Florent Krust et al.)
- 14:10–14:25: *Unravelling Corticospinal Contributions to Locomotion* (Charlotte Bichara et al.)
- 14:25–14:40: *Exploring Spinal Proprio-Motor Networks and Their Plasticity Using fMRI: From Fundamental Insights to Clinical Perspectives* (R Schlienger et al.)
- 14:40–14:55: *Title to be Announced* (Emmanuel Bourrinet et al.)

14:55–15:25: **Session 2: Regeneration and Disease** (Chair: Matilde Cordero-Erausquin)

- 14:55–15:10: *DCX-Derived Peptides Promote Axon Central Nervous System Repair* (Racha Al Tannir et al.)
- 15:10–15:25: *Repetitive Trans-Spinal Magnetic Stimulation Promotes Tissue Repair and Functional Recovery in a Focal Model of Spinal Cord Demyelination* (Fannie Semprez et al.)

15:25–16:00 : **Break** (35 min)

16:00–17:00 : Session 3: Spinal Cord Injury and Neuromodulation (Chair: Homaira Nawabi)

- 16:00–16:15: *Na^{+}/K^{+}-ATPase Dysfunction via Calpain-1 Fuels Motoneuron Hyperexcitability and Spasticity after a Spinal Cord Injury* (Nejada Dingu et al.)
- 16:15–16:30: *A New Paradigm of Spinal Magnetic Stimulation and Combined Therapies for Respiratory Recoveries after Cervical SCI* (Isabelle Vivodtzev)
- 16:30–16:45: *Effects of Anode Placement and Pulse Width on Upper-Limb Muscles Recruitment During Cervical Transcutaneous Spinal Cord Stimulation in Able-Bodied Individuals* (Nabila Brihmat et al.)
- 16:45–17:00: *Photobiomodulation Effects on Acute Neuroinflammation after Spinal Cord Injury* (Elsa Levy et al.)

17:00–17:30: **Session 4: Cellular and Molecular Insights into Motoneuron Pathology** (Chair: Cédric Raoul)

- 17:00–17:15: *Functional Analysis of New Molecular Markers of Motoneurons Vulnerable to Amyotrophic Lateral Sclerosis* (Issa Y et al.)
- 17:15–17:30: *Spinal Motoneuron Excitability Is Homeostatically-Regulated through β-Adrenergic Neuromodulation* (Guillaume Caron et al.)

17:30: **Networking Session**

SEROTONERGIC NEURONS OF THE CAUDAL RAPHE: DESCENDING CONNECTIVITY AND CONTRIBUTION TO SKILLED LOCOMOTION IN MICE

By

Yahia M.*[1], Giorgi A.*[1,2], Perreault M.-C.**[2], Bouvier J.**[1]

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*Equal first author contribution. **Equal last author contribution.

A role of serotonin (5-HT) in modulating the spinal locomotor circuits has long been inferred, yet the exact contribution to behavior and mechanisms of action of specific spinally projecting 5-HT neurons remains poorly understood. This owes, at least in part, to the positioning of spinally-projecting 5-HT neurons in multiple brainstem regions that also house other descending cell types. In this study, we genetically and spatially targeted the 5-HT neurons of the caudal raphe in the mouse and examined their connectivity and function specifically, using ex vivo electrophysiology, ex vivo and in vivo optogenetic manipulations, and anterograde tracings. Firstly, we demonstrate that caudal raphe 5-HT neurons innervate, already postnatally, the ventral laminae of the lumbar spinal cord where core circuits for locomotion reside. Functionally, optogenetic activation of the caudal raphe 5-HT neurons in the neonatal ex vivo brainstem-spinal cord preparation does not recruit lumbar motoneurons, but significantly inhibits their sensory-evoked responses. This suggests a potential role for caudal raphe 5-HT neurons in gating sensory afferent information rather than directly driving movement. Secondly, we tested this hypothesis in vivo by optogenetically manipulating the activity of caudal raphe 5-HT neurons during various locomotor tasks, in adult mouse. Our results show no alteration in gross locomotor features (e.g., speed or orientation) in an open field-test. However, we found that both the photo-activation and photo-inhibition of these neurons significantly disrupted the paw placement accuracy on a horizontal ladder test, indicating that caudal raphe 5-HT neurons might be specifically required for fine and adaptive limb control. Together, these findings unveil the necessity of a caudal raphe-mediated 5-HT modulation of sensory information processing in spinal motor networks for adaptive and skilled locomotion.

SK3 CHANNELS WORK IN TANDEM WITH T-TYPE CA^{2+} CHANNELS TO GATE RHYTHMOGENESIS WITHIN THE CENTRAL PATTERN GENERATOR FOR LOCOMOTION IN MICE

By

Krust F.[1], Brocard C.[1], Trouplin V.[1], Brocard F.[1,2]

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The rhythmogenic core of the spinal locomotor network harbors pacemaker bursting cells driven by the persistent sodium current (I_{NaP}), with ionic mechanisms of their emergence still undefined. Here, we show that blocking small-conductance calcium-activated potassium (SK) channels with apamin converts half of tonic spiking interneurons of the central pattern generator (CPG) into I_{NaP}-dependent rhythmic bursters. Immunohistochemistry revealed SK2 and SK3 channel clusters in interneurons within the locomotor CPG region. Consistently, inhibition of SK2 and SK3 with tamapin replicated the effects of apamin. To distinguish their individual contributions, targeted knockdown experiments showed SK3 silencing, but not SK2, induced oscillations in one-third of cells. Blocking T-type Ca^{2+} channels (mibefradil, nickel) promoted bursting, unlike L-type (nifedipine) or P/Q-type (ω-Agatoxin IVA) indicating T-type Ca^{2+} influx mainly regulates SK3 to control pacemaker bursting in the CPG. Finally, enhancing SK channel activity at the CPG level with 1-EBIO abolishes both bursting and locomotor-like rhythmic activity, suggesting the SK3/T-type Ca^{2+} interaction as a critical partnership for locomotor rhythmogenesis.

UNRAVELLING CORTICOSPINAL CONTRIBUTIONS TO LOCOMOTION

By

Bichara C.[1], Delbecq G.[1], Favier L.[1], Isope P.[1], Valera A.[1], Cordero-Erausquin M.[1]

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Despite decades of research across multiple species, the precise function of the sensorimotor cortex in regulating movement remains under investigation. Motor cortex neurons are thought to encode various aspects of movement, such as initiation and finer control of skilled behaviors. However, the specific contributions of corticospinal neurons (CSn), which form the most direct pathway for conveying motor signals, remain unclear. Although our recent data suggest that hindlimb CSn activation, while inducing motor output, primarily serves to gate lumbar sensory information, a key process for movement adaptation and coordination, the precise timing and consequence of their activation *in vivo* in freely moving mice remains unclear. By combining kinematic analysis and virus-mediated circuit perturbations, we aim to pinpoint crucial periods of CSn activity whose disruption leads to task-specific motor impairments. Furthermore, we recorded their activity through in vivo electrophysiological recordings in freely moving mice, identifying CSn through optotagging, to explore their role during incremental challenges in locomotor tasks. Our findings demonstrate that perturbing CSn activity directly impacts locomotor kinematics, even during basic locomotion. Additionally, we identify that a significant proportion of neurons in the somatosensory cortex exhibit phase-dependent activity correlated with several locomotor phases, while others have their activity locked to the beginning of the following stride. Our results highlight the dynamic role of corticospinal neurons in motor control, as they can both encode the ongoing locomotion and anticipate what is coming next, in a task-specific manner.

EXPLORING SPINAL PROPRIO-MOTOR NETWORKS AND THEIR PLASTICITY USING FMRI: FROM FUNDAMENTAL INSIGHTS TO CLINICAL PERSPECTIVES

By

Schlienger R., Kavounoudias A.

Collaborators: Landelle C., Hernandez-Charpak S., Pinzon D.M., Sein J., Nazarian B., Anton J.L., Courtine G.

Through spinal and cerebral pathways, muscle proprioception enables perception and control of movement. Proprioceptive afferents relay information of muscle stretch from the muscle spindles to the spinal cord, where direct connections between Ia afferents and motor neurons form the basis of the myotatic reflex. This sense can be manipulated using muscle tendon vibration, which selectively activates primary endings of muscle spindles and induces kinesthetic illusions without actual movement [Kavounoudias et al., 2023]. While proprioceptive integration has been widely investigated at the human cerebral level using non-invasive neuroimaging approach, its spinal mechanisms remain less non-invasively explored. Post-mortem studies have mapped spinal cord anatomy, while its functional properties have been explored via electrophysiology, invasive epidural stimulation, and clinical observations. In the past decade, spinal functional MRI (fMRI) has overcome key technical challenges, emerging as a powerful, non-invasive tool for studying spinal circuits [Landelle et al., 2021]. In this context, we conducted two innovative studies in healthy participants, combining spinal fMRI with targeted muscle tendon vibration to investigate spinal proprioceptive circuits. Our findings reveal distinct activation patterns depending on the stimulated muscle (tested on both upper and lower limbs), consistent with existing myotome maps, while also highlighting significant overlaps, multi-segmental innervation, and high inter-individual variability. Additionally, we contributed to the development of a novel nerve root segmentation tool integrated into the Spinal Cord Toolbox, enabling individualized analyses and improving the spatial accuracy of functional localization [Valošek et al., 2024]. Finally, we explored proprio-motor plasticity at the lumbar level, demonstrating increased activations after two weeks of targeted proprioceptive training, particularly at spinal levels corresponding to the trained muscles. These findings pave the way for non-invasive, longitudinal investigations of spinal sensorimotor circuits using spinal fMRI. Continuous advancements in acquisition and analysis tools further enhance the clinical potential of this approach, particularly for assessing circuit integrity after spinal cord injury [Rowald et al., 2022] and for understanding reorganization processes following limb amputation (ongoing project)

DCX-DERIVED PEPTIDES PROMOTE AXON CENTRAL NERVOUS SYSTEM REPAIR

By

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Developing effective therapeutic strategies for central nervous system (CNS) regeneration remains a significant challenge. Unlike other regenerative processes, CNS axons encounter unique inhibitory barriers that often result in irreversible functional losses. Recent studies have elucidated key molecular mechanisms underlying neuronal repair and enabled genetic modulation of pro-growth pathways. However, a major roadblock remains: transitioning from the identification of critical factors to developing therapeutic strategies applicable to patients. In this study, we investigated the potential of the doublecortin protein (DCX), a critical regulator of cytoskeletal organization and neural repair, as the scaffold for an innovative therapeutic approach.

Building on our previous work demonstrating that DCX is both neuroprotective and pro-regenerative, we developed a comprehensive library of peptidomimetics derived from its functional domains. Our investigation began with embryonic primary cultures, where we optimized peptide concentrations to achieve effective cell penetration while minimizing toxicity. Several peptides significantly increased axon length *in vitro*, prompting the selection of the most promising candidates for further evaluation. Subsequent *ex vivo* studies using adult retina explant cultures revealed that certain peptides produced notably greater axon lengths and densities compared to untreated controls. *In vivo* validation with an established optic nerve crush model confirmed that these peptides robustly promoted axonal regeneration beyond the lesion site, marking a critical milestone toward functional recovery. Similarly, *in vivo* the peptides also enhanced neuronal survival and reduced neuro-inflammation following optic nerve injury, thereby highlighting their neuroprotective influence.

These experiments yielded a promising set of high-value peptides for CNS regeneration, and we are actively expanding our library with additional candidates. Following these encouraging results, we evaluated the peptides in a spinal cord injury model to assess their ability to induce sprouting and regeneration in this more challenging context. Collectively, our results underscore the potential of DCX-based peptidomimetics as a novel strategy to overcome CNS regeneration barriers. Future efforts will focus on refining peptide formulations and delivery methods.

REPETITIVE TRANS-SPINAL MAGNETIC STIMULATION PROMOTES TISSUE REPAIR AND FUNCTIONAL RECOVERY IN A FOCAL MODEL OF SPINAL CORD DEMYELINATION

By

Semprez F.[1], Ziane I.[1], Istre I.[1], Du A.[1], Dupuis L.[1], Moncomble L.[1], Neveu P.[1], Raimond C.[1], Guérout N.[1]

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According to the World Health Organization (WHO), more than 15 million people worldwide are living with a spinal cord injury (SCI), with an estimated 250,000 to 500,000 new cases reported each year. SCIs represent a significant global health burden due to their profound impact on patient health and quality of life. While the majority of SCIs result from traumatic events, approximately 10% are non-traumatic, arising from cellular dysfunctions that may be associated with tumors, inflammation, or infections.

Transverse myelitis (TM) is a rare, non-traumatic disorder of the central nervous system (CNS), characterized by inflammation of the spinal cord (SC) affecting one or more vertebral segments — most commonly within the thoracic region in 70% of cases. This inflammation triggers progressive cellular damage, disrupting ascending and descending neural communication between the brain and the body. Consequently, TM often leads to partial or complete loss of motor, sensory, and/or autonomic functions.

Currently, available medical and technological interventions provide only partial and temporary improvements in the quality of life for patients with SCI. In our laboratory, we are investigating a non-invasive therapeutic strategy: repetitive trans-spinal magnetic stimulation (rTSMS). In previous work using a traumatic SCI model, we demonstrated that rTSMS modulates various cellular populations at the lesion site, influencing glial scar formation, reducing inflammation and demyelination, and promoting neuronal survival and regeneration.

We hypothesized that rTSMS could exert similar beneficial effects in non-traumatic SCI, such as TM. To test this, we developed a mouse model of TM, in which half of the animals received rTSMS treatment. Locomotor performance was assessed using automated behavioral tests, and histological analyses were performed to evaluate tissue responses. Our results demonstrated that rTSMS promotes both functional recovery and tissue repair following demyelinating inflammatory injury.

Moreover, RNA sequencing analyses revealed sex-specific responses to rTSMS treatment. In male mice, rTSMS enhanced the expression of gene ontology (GO) classes associated with myelination and axonal regeneration. In contrast, in female mice, rTSMS predominantly modulated immune-related pathways, particularly those involving the adaptive immune response and T lymphocytes.

Overall, this research provides new evidence that rTSMS promotes functional and molecular recovery in a preclinical model of demyelination and supports its potential application as a therapeutic strategy for non-traumatic SCI in humans.

NA^+/K^+-ATPASE DYSFUNCTION VIA CALPAIN-1 FUELS MOTONEURON HYPEREXCITABILITY AND SPASTICITY AFTER A SPINAL CORD INJURY

By

Dingu N.[1], Barbey T.[1], Krust F.[1], Brocard C.[1], Liabeuf S.[1], Bras H.[1], Bos R.[1], Brocard F.[1]

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Spasticity, marked by stiffness and involuntary muscle contractions, typically arises weeks to months post-spinal cord injury (SCI), hindering *in vitro* studies in adults. To overcome this limitation, we developed a neonatal mouse model in which SCI is performed at birth, enabling *in vitro* investigation of spasticity mechanisms. Within 4-5 days post-injury, mice exhibited hallmark signs of spasticity including spontaneous unvoluntary muscle contractions (spasms) and exaggerated reflexes (hypereflexia). Isolated spinal cords displayed heightened excitability below the lesion, amplifying both spontaneous and sensory-driven motor activities consistent with core spasticity behaviors. At the cellular level, motoneurons exhibited marked hyperexcitability, characterized by a reduced rheobase and a depolarized resting membrane potential (RMP). Notably, the RMP depolarization was insensitive to tetrodotoxin (TTX), suggesting that it is independent of both network activity and persistent sodium currents. Given the central role of the Na^+/K^+-ATPase (NKA) in maintaining RMP, we assessed its function using ouabain, a specific NKA inhibitor. Ouabain induced a greater depolarization in control motoneurons compared to SCI motoneurons, indicating impaired NKA function following injury. Building on our previous findings that calpain-I activation contributes to motoneuron hyperexcitability after SCI (Brocard et al., 2016; Plantier et al., 2019; Kerzonkuf et al., 2024), we hypothesized that NKA dysfunction might result from calpain-I activity. To test this, we employed a gene approach to selectively downregulate calpain-I in lumbar motoneurons. This intervention preserved NKA function by normalizing RMP, thereby reducing spinal network hyperexcitability, and alleviating spasticity in neonatal mice following SCI.

Brocard C, Plantier V, Boulenguez P, Liabeuf S, Bouhadfane M, Viallat-Lieutaud A, Vinay L, Brocard F. (2016). Cleavage of Na(+) channels by calpain increases persistent Na(+) current and promotes spasticity after spinal cord injury. *Nat Med*, 22, 404–411.

Plantier V, Sanchez-Brualla I, Dingu N, Brocard C, Liabeuf S, Gackière F, Brocard F. (2019). Calpain fosters the hyperexcitability of motoneurons after spinal cord injury and leads to spasticity. *eLife*, 8, e51404.

Kerzonkuf M, Verneuil J, Brocard C, Dingu N, Trouplin V, Ramirez Franco JJ, Bartoli M, Brocard F, Bras H. (2024). Knockdown of calpain1 in lumbar motoneurons reduces spasticity after spinal cord injury in adult rats. *Mol Ther*, 32, 1096–1109.

A NEW PARADIGM OF SPINAL MAGNETIC STIMULATION AND COMBINED THERAPIES FOR RESPIRATORY RECOVERIES AFTER CERVICAL SCI

By

Vivodtzev I., Chen W.

NeAR Team, "Neural Adaptation and Repair", Dev2A, CNRS UMR8263, Inserm U1345, Institute of Biology Paris Seine, IBPS, Sorbonne Université, Paris, France

A majority of spinal cord injuries (SCI) occur at the cervical level, causing locomotor paralysis, but also dramatically altered respiratory capacity. Injuries at C4 or higher often lead to ventilator reliance, lowering quality of life and increasing mortality. Mechanical ventilation is the primary solution and alternative methods are limited due to muscle weakness of reduced phrenic conduction.

We have recently developed an innovative system to non-invasively stimulate extra diaphragmatic muscles (intercostal and abdominal muscles) that is synchronized with breathing (rSynES, patented algorithm Algostim). However, recoveries are partial and need to be combined with repairing strategies of the spinal cord and motoneuron function. In this perspective, through the doctoral work of Mrs Wei Chen and with ongoing collaboration with Dr Stéphane Vinit (Versailles Paris Saclay University), we first analyzed the perineuronal sate of injured spinal cord in a pre-clinical model of SCI and then compared its state after repetitive magnetic stimulation (rMS) as a non-invasive method to reduce neuroinflammation and promote neural repair. Our recent findings suggest that, when applied at the cervical spinal cord, it can induce recovery in tidal volume and diaphragm activity after a C3/4 hemi-contusion in mice.

In extension to this work, our current step is to explore, in a rat model, a new magnetic stimulation device, based on adapted-small coils and to apply a low intensity rMS (LI-rMS); weaker pulses (micro- to millitesla). This approach can modulate neural function in brain and hence could induce plasticity specifically at the spinal cord level, while offering potential for easier clinical application in the future.

In this presentation, current and future projects will be presented aiming at increasing spinal neuromodulation to promote neuroplasticity and improve diaphragm function, offering an alternative to mechanical ventilation. Our goal is to come up with proof-of-concept studies of the efficiency of magnetic stimulation alone and combined with other therapeutic approaches. This is made possible by the collaboration of investigators now working as a unified team (Drs Vivodtzev, Rachel Sherrard and Fatiha Nothias) who each brings specific and complementary technological expertise to create a highly innovative multidisciplinary synergy.

EFFECTS OF ANODE PLACEMENT AND PULSE WIDTH ON UPPER-LIMB MUSCLES RECRUITMENT DURING CERVICAL TRANSCUTANEOUS SPINAL CORD STIMULATION IN ABLE-BODIED INDIVIDUALS

By

Brihmat N.[1], Colas Z.[1], Corbin N.[2], Cassoudesalle H.[3], Minassian K.[4], Hofstötter U.[4], Rowald A.[5],[6], Wagner F.[1]

Cervical transcutaneous spinal cord stimulation (tSCS) has recently been shown to promote upper- limb motor recovery after spinal cord injury (SCI). Yet, its underlying mechanisms remain unclear. Although seminal studies have shown that tSCS applied at the lumbosacral spinal cord elicits posterior-root muscles reflexes, recent reports suggest that lumbar and cervical tSCS may act differently. In a clinical study approved by a French ethical research committee, we aim to gain insights into tSCS mechanisms by investigating upper-limb muscle electromyographic responses to different tSCS configurations in able-bodied individuals. Preliminary data were obtained in 11 able-bodied individuals. Monophasic tSCS pulses (200, 500 or 1000 µs pulse width) were delivered every 5 s at increasing stimulation amplitude with the cathode placed at the C5/C6 or C7/T1 vertebrae and the anodes placed bilaterally at one of the following locations: medial clavicle, lateral clavicle, or iliac crest. Evoked responses peak-to-peak amplitudes were measured from bilateral upper-limb muscles and were used to obtain muscle- and condition- specific recruitment curves and response thresholds. Differences in recruitment curve profiles and response thresholds between the different conditions were consistently observed across participants. Anodes placed over the lateral clavicles were associated with the overall lowest response thresholds. Not surprisingly, higher pulse widths were associated with lower response thresholds. These results highlight the influence of anode location on the recruitment of upper-limb muscles during cervical tSCS. Other stimulation parameters could also have significant influence and need to be explored. MRI acquisitions may help to understand the recruitment of different neural structures by cervical tSCS.

PHOTOBIOMODULATION EFFECTS ON ACUTE NEUROINFLAMMATION AFTER SPINAL CORD INJURY

By

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Background: Non-invasive photobiomodulation therapy (PBMT), employing specific infrared light wavelengths to stimulate biological tissues, has recently gained attention for its application to treat neuroinflammation in various pathologies. Using a preclinical mouse model of Spinal Cord Injury (SCI), we aimed to uncover the cellular effects of early and transient PBMT on both resident and peripheral inflammatory cells in a post-traumatic context. A dorsal glass window was implanted immediately after spinal unilateral dorsal hemisection in aged “AMU-Neuroinflam” triple fluorescent reporter mice (> 70 weeks old) (El Waly et al. 2021). Longitudinal intravital 2 Photon microscopy was then applied on the spinal cord of the same anesthetized mice to simultaneously image dorsal sensory and proprioceptive axons, activated resident microglia, as well as circulating or infiltrated peripheral inflammatory cells (neutrophiles and monocytes). Cellular densities were repeatedly evaluated in the same superficial regions of interest on days 0, 3 and 7 after trauma.
One group of animals received 6 min daily dorsoventral PBMT (Escarrat et al. 2024) for 5 consecutive days starting 2 hours after injury (n=3) while the other one remained untreated (n=3). The same neuroinflammatory processes were also characterized in the deep ventral regions of the spinal cord on day 7 using fixed coronal slices centered around the lesion epicenter. We found that early PBMT triggered a more rapid accumulation of peripheral neutrophiles and monocytes as compared to the untreated condition. In the blood vessels, densities of circulating cells were transiently increased on day 3 for the treated group (74 versus 120 cells/0.01mm). This early boost promoted a corresponding transient accumulation in the spinal parenchyma (54 versus 94 cells/0.01mm). However, 3 days after the end of PBMT (D7) this inflammatory response increased to similar levels in both conditions. Effect of PBMT was similar on the density of resident microglia whose activation was transiently boosted on day 3 (11 versus 43 cells/0.01mm). It persisted only on the contralateral side on D7 (77 versus 114 cells/0.01mm) after treatment had been stopped. At the neuronal level at D3, axonal density that represented 4% of spinal cord volume for the control group instead reached 9,3% for the treated one, supporting the idea of a neuroprotective effect. The axonal density remained stable in both conditions at D7 (5,2% versus 9,6%)
Keywords: Spinal Cord Injury; Neuroinflammation; Photobiomodulation therapy.

FUNCTIONAL ANALYSIS OF NEW MOLECULAR MARKERS OF MOTONEURONS VULNERABLE TO AMYOTROPHIC LATERAL SCLEROSIS

By

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Abstract:
Modification of motoneurons' electrical activity is a key factor in amyotrophic lateral sclerosis (ALS) disease progression. Experimental evidence has revealed a motoneuron-type vulnerability in ALS, beginning with the low excitability fast fatigable (FF) motoneurons, while the high excitability slow (S) motoneurons are preserved. These observations have led to the hypothesis that the high task demand of the FF motoneurons is responsible for their greatest vulnerability. To broaden our understanding of the role of excitability in selective degeneration and to improve the functional characterization of motoneurons types, we performed single-cell transcriptomic analysis using the patch-seq method on FF and S motoneurons subtypes, identified through patch-clamp electrophysiology [1] [2]. The expression of voltage-gated channels was analyzed in six FF motoneuron RNA banks and six S motoneuron RNA banks. Cacna2d3, a gene encoding CaVα2δ3, a regulatory subunit of high voltage activated calcium channels, was significantly upregulated in the FF motoneurons. Due to its high expression in ALS vulnerable motoneurons, we are currently investigating its role in motoneuron physiology and under ALS pathological conditions. In Cacna2d3-/- motoneurons, we show a drastic change in the subcellular localization of the P/Q type calcium channel CaV2.1, the major channel involved in spinal neurotransmission, suggesting a regulation of its function by the CaVα2δ3 subunit. Consistent with this results, motor behavioral studies revealed an increased endurance during locomotor tasks in the knock-out mice. These mice also demonstrated heightened sensitivity to exhaustion during physical effort. The functional significance of Cacna2d3 in neurotransmission and firing properties of motoneurons will next be investigated by electrophysiological studies, as well as its impact on ALS progression by crossing the knock-out mice with a SOD1G93A mouse line.

References:
[1] Soulard C, Salsac C, Mouzat K, et al. Spinal Motoneuron TMEM16F Acts at C-boutons to Modulate Motor Resistance and Contributes to ALS Pathogenesis. Cell Rep. 2020;30(8):2581-2593.e7.

[2] Fuzik J, Zeisel A, Máté Z, et al. Integration of electrophysiological recordings with single-cell RNA- seq data identifies neuronal subtypes. Nat Biotechnol. 2016; 34(2):175-183.

Keywords: Motoneuron vulnerability, Calcium channel, Electrical activity
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SPINAL MOTONEURON EXCITABILITY IS HOMEOSTATICALLY-REGULATED THROUGH β-ADRENERGIC NEUROMODULATION

By

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Modulation (up- or down-regulation) of motoneuron (MN) excitability and synaptic excitation constitutes an important entry point to affect MN degeneration in amyotrophic lateral sclerosis (ALS). We have previously demonstrated that chronic chemogenetic interventions targeting excitability and PKA signaling can exert profound beneficial effects on disease burden in ALS MN. To achieve a comparable upregulation of PKA signaling and MN firing, we targeted the PKA-coupled adrenergic ß2/ß3 receptors using selective, brain-permeant agonists. In vivo MN electrophysiological recording revealed a substantial increase in MN firing rate following acute administration of these agonists and intracellular iontophoretic injection of a PKA activator. However, these effects disappeared with chronic ß2/ß3 receptors activation due to homeostatic regulation of Gs coupled receptors. Preliminary results are also presented on alternative approaches aimed at upregulating PKA activity independently of Gs coupled receptors.

Emmanuel Bourrinet

Title and Abstract to be Announced