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**From cerebral palsy to developmental coordination disorder: development of preclinical rat models corresponding to recent epidemiological changes**

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## **Abstract**

Cerebral palsy (CP) is a complex syndrome of various sensory, motor and cognitive deficits. Its prevalence has recently decreased in some developed countries and its symptoms have also shifted since the 1960s. From the 1990s, CP has been associated with prematurity, but recent epidemiologic studies show reduced or absent brain damage, which recapitulates developmental coordination disorder (DCD). In previous studies, we developed a rat model based on mild intrauterine hypoperfusion (MIUH) that recapitulated the diversity of symptoms observed in preterm survivors. Briefly, MIUH led to early inflammatory processes, diffuse brain damage, minor locomotor deficits, musculoskeletal pathologies, neuroanatomical and functional disorganization of the primary somatosensory (S1) cortex but not in the motor cortex (M1), delayed sensorimotor reflexes, spontaneous hyperactivity, deficits in sensory information processing, and memory and learning impairments in adult rats. Adult MIUH rats also exhibited changes in muscle contractile properties and phenotype, enduring hyperreflexia and spasticity, as well as hyperexcitability in the sensorimotor cortex. We recently developed a rat model of DCD based on postnatal sensorimotor restriction (SMR) without brain damage. Briefly, SMR led to digitigrade locomotion (i.e., “toe walking”) related to ankle-knee overextension, degraded musculoskeletal tissues (e.g., gastrocnemius atrophy), and lumbar hyperreflexia. The postnatal SMR then led to secondary degradation of the hind-limb maps in S1 and M1 cortices, altered cortical response properties and cortical hyperexcitability, but no brain damage. Thus, our 2 rat models appear to recapitulate the diversity of symptoms ranging from CP to DCD and contribute to understanding the emergence and mechanisms underlying the corresponding neurodevelopmental disorders. These preclinical models seem promising for testing strategies of rehabilitation based on both

physical and cognitive training to promote adaptive brain plasticity and to improve physical body conditions.

## **Introduction**

The most common physical disability in children, cerebral palsy (CP), involves a group of disorder of movement and posture and of motor function, including spasticity (85-91% of cases) and is caused by a lesion, interference or abnormality that originates in the immature brain [1–4]. Refer to [1,5] for a comprehensive definition of CP. Nonetheless, the complete path to CP is unclear in about 80% of cases. However, risk factors occur before, at and after birth and include preterm birth, multiple births, hypoxia-ischemia, infection, intrauterine growth retardation, indicators of intrapartum compromise, neonatal encephalopathy and congenital anomalies that usually converge toward perinatal chronic inflammation [2,3,6,7]. Comorbidities and functional limitations are common and invalidating, including chronic pain (75%), cognitive impairments along with sensory and perceptive deficits (50%), epilepsy (35%), musculoskeletal pathology (28%), and behavioral disorders (26%) [3,4].

From the 1960s to 2010s, the prevalence of CP has been fluctuating around 2.1‰, although declining trends have been reported in recent years from Europe, Japan and Australia [2,8]. The symptoms of CP have also shifted over the last decades. Briefly, before the 1990s, CP symptoms broadly included cystic brain damage associated with severe sensorimotor disorders and behavioral/cognitive impairments in at least 50% of cases. From the early 1990s, the symptoms of CP gradually evolved toward diffuse gray and whitematter injury (WMI), mainly associated with moderate to severe sensorimotor disorders and behavioral/cognitive deficits (i.e., learning impairments, attention disorder and hyperactivity deficit [ADHD] and executive functions) in most cases. These changes appeared in relation to an increasing population of survivors of very low birth and very/extremely prematurity and correspond to encephalopathy of prematurity (EP), usually associated with placental

inflammation as a major cause of spontaneous preterm delivery [2,4,9,10]. In the first part of this opinion paper, we summarize a series of prior studies devoted to intrauterine hypoperfusion that reproduces growth retardation at birth and the variety of EP and CP symptoms to better understand the underlying mechanisms.

Recent epidemiologic studies of CP show a tiny, gradual decrease in its prevalence and from reduction to the absence of brain damage in term babies and very and extremely preterm babies. This reduction seems associated with minor sensorimotor deficits associated with ADHD and mild to severe deficits in executive functions and learning abilities [2,5,8,11], corresponding to developmental coordination disorder (DCD), present in about 5% to 6% of school-age children [12,13]. In the *International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> Revision*, DCD is referred to as a specific developmental disorder of motor function [14]. Without apparent brain damage but reduced whitematter organization in the sensorimotor networks [15], patients with DCD show reduced ability to produce consistent movements, poor motor coordination and kinaesthetic acuity, and broad impairments in sensorimotor representations and perception, each reflected by disrupted central networks [12,16–18]. DCD usually co-occurs with one or more other neurodevelopmental disorders, such as ADHD, specific language impairment, learning disorders, autism spectrum disorder (ASD), and developmental dyslexia or reading disorder [12,17–19]. For instance, children with ASD also exhibit gross or fine motor abnormalities, motor learning deficiencies and difficulties executing sequences of actions [20]. According to some authors, CP could be a continuum of DCD [17,21]. In fact, most children with EP, CP, DCD or ASD show sensorimotor impairments, reduced physical activity and interactions with their environment, and atypical motor development [5,17,18,20,22]. The latter is usually detected as atypical spontaneous or general movements (GMs) in those with CP or DCD [17,22–24]. As compared with typical GMs, atypical GMs correspond to rigid and cramped-

synchronized and stereotyped movements that exhibit limited fluency, variation and complexity with increasing age [25]. Atypical, disturbed GMs appear to reflect impaired connectivity and functional organization of the brain [22,26]. Based on postnatal movement restriction, we developed a second animal model that provides limited and abnormal patterns of somatosensory inputs during development, which led to abnormal organization of the adult sensorimotor circuitry and enduring movement disorders, thus recapitulating most of the symptoms observed in DCD in children.

The present paper summarizes previous studies in which we developed animal models of EP based on mild intrauterine hypoperfusion (MIUH) or DCD originating from postnatal movement restriction during development. In this position paper, we emphasize the notion that neuromuscular interactions act as self-perpetuating cycles, in which the body and central nervous system (CNS) continuously interplay throughout refference and motor commands. The presence of atypical sensorimotor experience related to perinatal brain damage and/or abnormal sensory inputs to the immature brain leads to developmental maladaptive plasticity, which in turn may lead to long-lasting disturbed motor commands and outputs. These abnormal motor outputs in turn produce atypical refference and atypical sensorimotor experience that induce, maintain or even aggravate the neuroanatomical and/or functional disorganization of both the sensorimotor circuitry and CNS. Recently, Canu et al. (2019) emphasized that accurate rehabilitation should try to avoid such detrimental self-perpetuating cycles [27] and promote social, parental and cognitive interactions and with the environment in general.

### ***Animal model of cerebral palsy***

To produce intrauterine growth retardation in rats, we performed stenosis of uterine arteries by first using ligation at embryonic day 17 (E17) and then metal-coated coils wrapped

around intrauterine arteries at E17. In both procedures the blood flow perfusion in the placenta and fetus was reduced about 15% to 20% a few hours after stenosis and then returned to pre-stenosis levels at E20 [28–30]. Pups were delivered by spontaneous labor at E22 and those with weight < 5.5 g were considered growth retarded and part of the MIUH group [28,31–33]. Lower body weight persisted at postnatal day 56 (P56) after MIUH in both males and females but did not extend into adulthood (P90-100) [32].

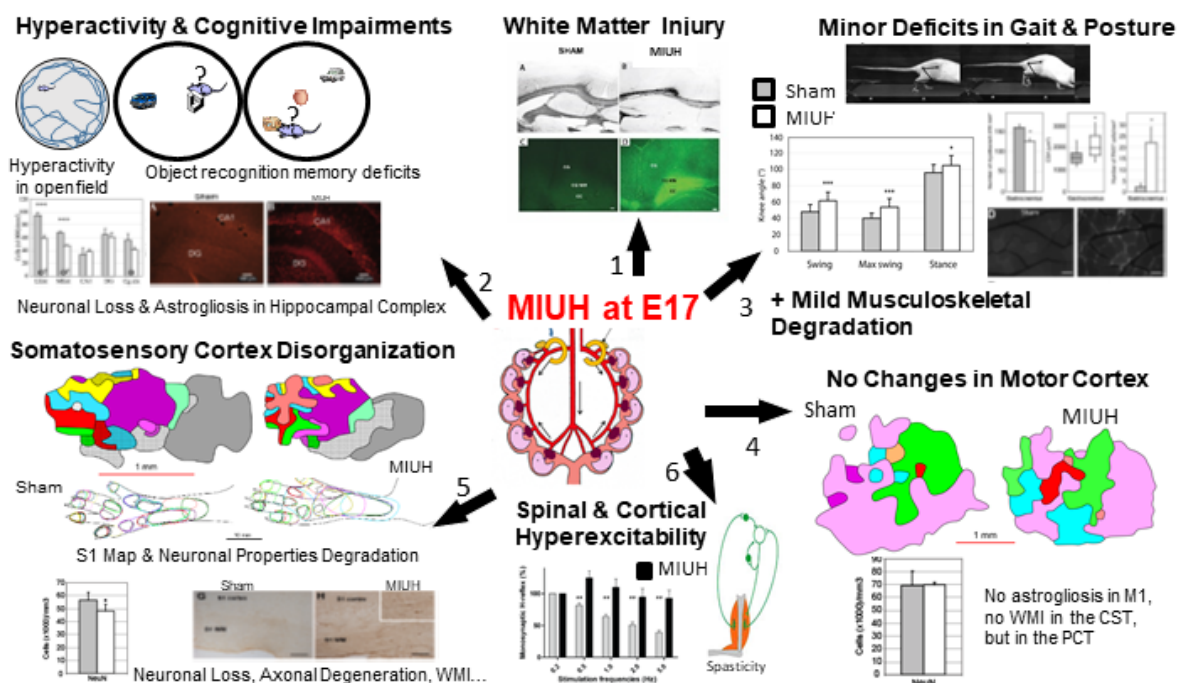
### *Brain damage*

MIUH at E17 led to myelination deficits in the corpus callosum and cingulum of rats from birth to P21 [31,34]. Hypomyelination and axonal degeneration persisted in the internal and external capsules, corpus callosum genu, and pontocerebellar tract and in white matter zones below the cingular and primary somatosensory (S1) cortices of adult MIUH rats (Fig. 1). No hypomyelination nor axonal degeneration was detected in white matter zones below the primary motor cortex (M1) or in the corticospinal tract. Degenerating axons were detected in the hippocampal CA3 region, lateral and medial entorhinal cortices and fornix but not in the prefrontal cortex. Massive astrogliosis was also observed in white matter associated with the cingular and S1 cortices, the hippocampal CA1, dentate gyrus, fornix, lateral and medial entorhinal cortices as well as enlargement of the lateral ventricles of adult MIUH rats [28,32,33,35]. The severity of hypomyelination in these adult rats was correlated with the gradient of growth restriction at birth [31,33,34].

The thickness of the cerebral cortex and corpus callosum was reduced in MIUH rats [28,33]. MIUH decreased neuronal densities in S1, particularly inhibitory interneurons, and decreased the height of cortical grey matter in adult rats. In contrast, M1 showed no structural changes [33]. MIUH at E17 decreased neuronal density in the lateral and medial entorhinal

cortices but not in the CA1, dentate gyrus of the hippocampus or cingulate cortex, in which the density of inhibitory interneurons was surprisingly increased [33,35].

Adult MIUH rats showed no obvious tissue damage, such as cystic and necrotic lesions or inflammatory cell infiltration [28]. In contrast, we found increased levels of inflammation-related chemokines and cytokines and ischemia-related proteins in placentas but only tendencies in MIUH fetuses at E20. We also found mRNA changes, indicative of incomplete axonal outgrowth and astrocyte dysfunction but little to no impairment of immature neurons and pre-oligodendrocytes in MIUH fetuses at E20 [28]. Common features observed with MRI in preterms with intrauterine growth restriction were diffuse gray and white matter injuries and astrogliosis in various brain areas and ventricular enlargement and were usually associated with detrimental neurological outcomes [10,36]. Prematurity and the various brain injuries appeared related to imbalanced inflammation during pregnancy [6,7].



*Behavioral and cognitive impairments*



MIUH at E17 induced spontaneous locomotor hyperactivity mainly in the early phase of open-field tests, deficits in short-term and long-term memory in object recognition tasks, and disturbances in encoding spatial configurations and object features in adult rats (Fig. 1). However, we found no deficits in spatial learning or spatial working memory in Morris water maze tests. In addition, the more the MIUH rats were growth-retarded at birth, the more they exhibited hyperactivity, degraded performances in memory tasks, astrogliosis in the fornix and decreased neuronal density in entorhinal cortices [35]. Associated with hippocampal and prefrontal cortex damage, these neurodevelopmental disorders are usually often encountered in preterm children in whom WMI, ADHD and/or CP develop [36,37]

#### *Sensorimotor disturbances*

For sham and MIUH rats, analyses of the 3D kinematics of locomotion on a treadmill for a speed of  $0.23 \text{ m}\cdot\text{s}^{-1}$  at P30 (juveniles) and P65 (young adults) showed comparable cadence and durations of the stance and swing during the stride. Despite apparent normal posture and gait, MIUH rats exhibited reduced length, amplitude and velocities of the foot during the stride phase when they were juvenile and young adults. Only adult MIUH rats showed a significant overextension of the knee and ankle that was compensated by an overflexion of the hip (Fig. 1). In addition, juvenile MIUH rats exhibited lower variations in many kinematic measures than age-matched controls, whereas with maturation, young-adult MIUH rats showed higher variations, suggestive of maturation deficits after MIUH [32]. Early WMI was strongly correlated with reduced motion range, movement complexity and variations and atypical GMs during development in preterm infants and children with CP [23,25].

Adult MIUH rats exhibited fewer myofibres overall, hypertrophy of the myofibres in the gastrocnemius and a greater variation in size of myofibers in the gastrocnemius (Fig. 1), rectus femoris and tibialis anterior [32]. They also exhibited changes in soleus muscle

contractile properties toward a lower twitch tension and the persistence of neonatal myosin heavy chain isoform, showing abnormal maturation of muscle properties and phenotype [29]. More satellite cells in the gastrocnemius after MIUH suggested a prior injury to that muscle and now a repair or regeneration process because the myofiber number was reduced [32]. We detected mild knee and ankle joint chondromalacia after MIUH that could result from an imbalance in muscle forces across joints [32], as observed in people with CP [38]. Such mild changes in joints and muscles and minor gait abnormalities have been reported in people with CP [39] and suggest the possible presence of spasticity.

To evaluate signs of spasticity and spasms in adulthood after MIUH, corresponding to hyperexcitability in the spinal circuitry, we assessed changes in Hoffmann reflex (H-reflex) [40–42]. In post-activation depression (PAD), the monosynaptic H-reflex decreased with increasing stimulation frequency in sham rats, whereas PAD after MIUH tended to increase (Fig. 1), which suggests the presence of hyperreflexia and likely signs of spasticity in adult MIUH rats [29,41–43]. However, MIUH produced no significant alterations of both functional organization of the motor hind limb maps and M1 neuronal properties. No neuroanatomical changes were detected in M1 and no sign of axonal degeneration in the corticospinal tract, a main efferent tract of M1 [33].

MIUH degraded the S1 neuronal properties and somatotopic maps, devoted to represent the hind-limb skin surfaces. This degradation was mainly characterized by a reduction in map size, enlarged and multiple receptive fields that encompassed several toes or pads simultaneously, leading to a topographic disorganization and a patchy representation in S1 (Fig. 1; see [33] for details). This disorganization appeared related to neuroanatomical changes in adult MIUH rats, such as lower densities of neurons, especially inhibitory interneurons, WMI below S1, astrogliosis and increased caspase reactivity (i.e., sign of inflammation), with no cystic lesions [33]. Abnormal lamination of the parietal cortex,

presumably due to premature disruption of the cortical subplate, was associated with gait disturbances in adult rats exposed to comparable MIUH at E17-18 [9]. In addition to adult lumbar hyperexcitability, MIUH led to increased extracellular concentration of glutamate in the sensorimotor cortex as compared with sham treatment, but the extracellular concentration of gamma-aminobutyric acid (GABA) did not differ between the 2 groups by using *in vivo* microdialysis. Relative to sham treatment, in MIUH rats, the level of vesicular glutamate transporter (vGLUT1) in the sensorimotor cortex was increased about 40% and that of vesicular GABA transporter (vGAT) was reduced about 15% [29], which suggests adult cortical hyperexcitability after MIUH.

#### *Early putative mechanisms*

Like in adulthood, MIUH at E17 led to early hyperreflexia reflected by increased stretch H-reflex a few days after birth (P4-P6), suggestive of signs of spasticity [29]. At least two mechanisms are widely considered responsible for such hyperreflexia: increased excitability in motoneurons and reduced inhibition, the so-called disinhibition, within the lumbar spinal network [44]. Disinhibition of the myotatic reflex seems to be caused by reduced expression of the active form of K<sup>+</sup>-Cl<sup>-</sup> cotransporter 2 (KCC2), which abnormally increases the intracellular concentration of chloride ions and reverses the effect of GABA from hyperpolarization to depolarization [43,44]. We found that MIUH decreased the expression of both inactive and active forms of KCC2, which induced early hyperreflexia and may reflect spasticity, like after spinal cord injury in neonate rats [44]. Early and enduring increased stretch reflex and the possible presence of spasticity may be the origin and persistence of the minor locomotor impairments found in adult MIUH [32].

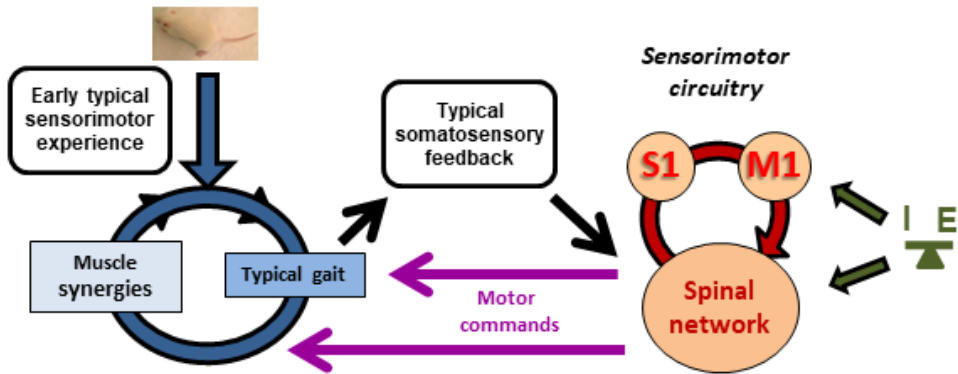
Preterm infants and children with CP exhibit neuroinflammation processes from *in utero* to postnatal life [6,7]. We also found that MIUH had a deleterious impact mainly for placenta

on the levels of proteins related to inflammation and ischemic/vascular injury [28]. Calpains, which are intracellular proteases activated by calcium influx during excitotoxicity, regulate cellular homeostasis, neuronal activity or apoptosis during development and in the mature CNS and appear crucial for typical neurodevelopment, including learning and memory [45]. Excessive calpain activity appears to degrade key proteins for neural function [32], such as KCC2 in the hippocampus and cortical layer IV after comparable MIUH at E18 [46]. Indeed, recent studies have shown the deleterious contribution of excess calpain activity to cleave KCC2, which becomes inactive and thus contributes to hyperexcitability [47], and to upregulate the persistent sodium current in motoneurons [48]. This can lead to the development of hyperreflexia, and likely spasms and spasticity, as shown after spinal cord injury [48]. Of note, postmortem cerebral samples from human preterm infants with WMI showed loss of KCC2 expression [49].

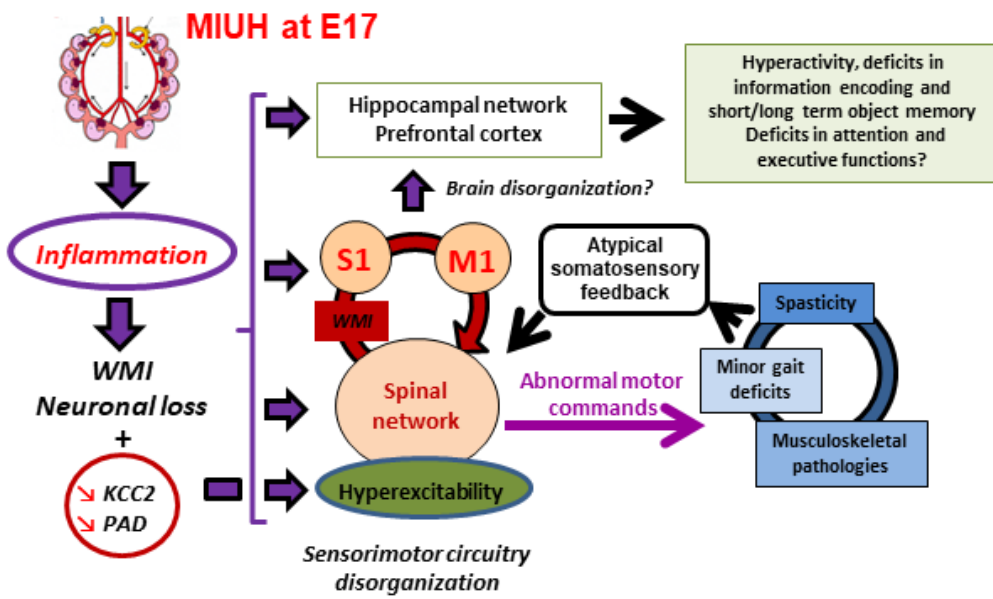
Thus, we suppose that MIUH-related intrauterine inflammation induces overactivity of calpains, which reduces the expression/function of KCC2 from postnatal to adult stages and leads to early and enduring hyperreflexia and likely to signs of spasticity and spasms, probably at the origin of the minor locomotor disorders and contractile dysfunctions observed in juvenile and adult MIUH rats (Fig. 2B). Then, hyperreflexia, musculoskeletal pathologies and gait deficits interplay to maintain each disorder and produce abnormal proprioceptive feedback/reafference to the immature spinal network, and finally to the S1 cortex, thus leading to disorganized sensorimotor circuitry from development to adulthood (Fig. 2B; [29]). In addition, MIUH reduced KCC2 expression/function [47] and altered the proliferation of oligodendrocyte precursors [6], which both may contribute to WMI, as found below the S1 cortex. In addition to atypical reafference, postnatal WMI below S1 may also contribute to the disorganization of the S1 maps and sensorimotor circuitry (Fig. 2B) through inappropriate information synchrony and maladaptive plasticity, which we previously postulated [50]. In

addition to early lumbar hyperreflexia, such disorganization of the sensorimotor circuitry may in turn produce abnormal motor commands, which in turn may contribute to induce, maintain, or even aggravate altered muscle synergies, maturation and functional properties, as well as locomotor disturbances and musculoskeletal histopathology, into self-perpetuating cycles (Fig. 2B). Therefore, MIUH-related neuroinflammation may contribute to the structural and functional disorganization of the sensorimotor circuitry, including WMI, and to the brain disorganization including the hippocampal complex and prefrontal cortex, thereby leading to behavioral and cognitive impairments observed after MIUH (Fig. 2). Thus, MIUH appears to recapitulate the variety of symptoms observed in premature children in whom WMI, ADHD, EP and in some cases CP develop.

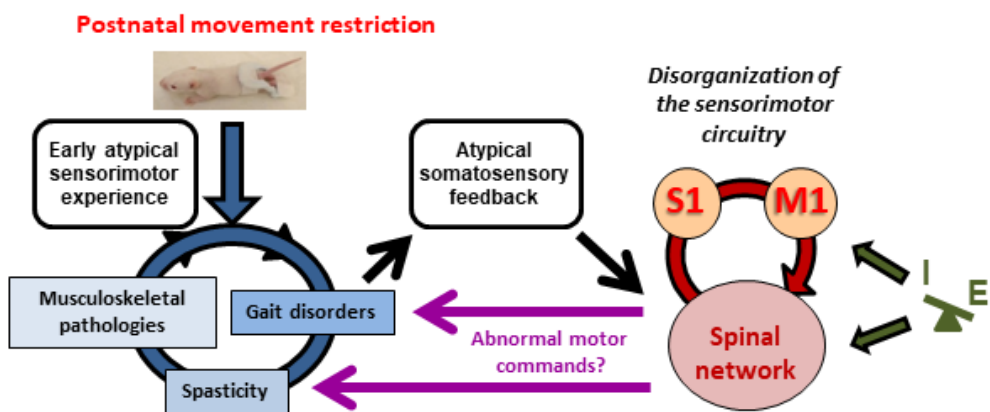
**A**



**B**

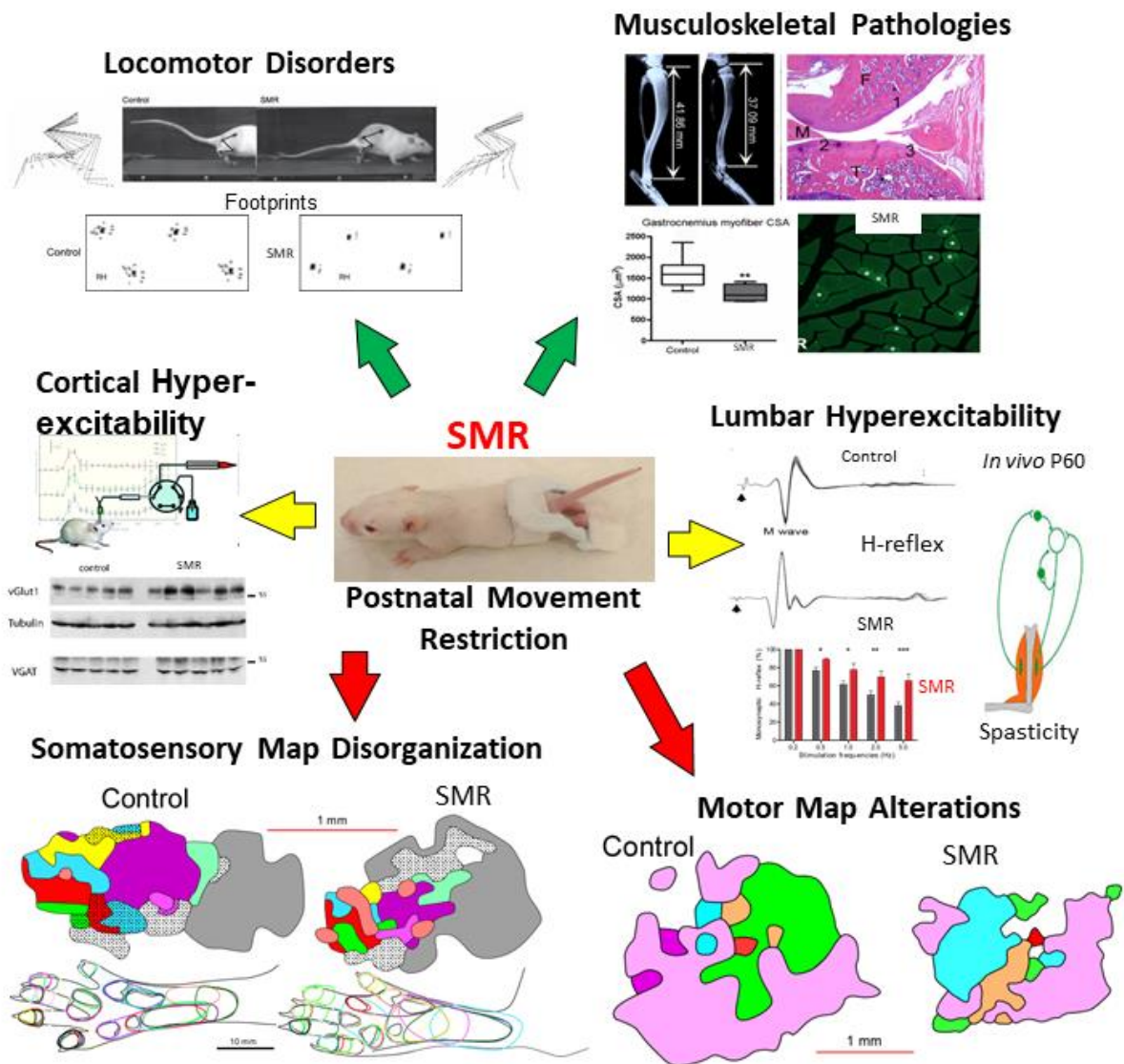


**C**



### *Animal model of developmental coordination disorder*

Rat pups were submitted to postnatal movement deprivation leading to sensorimotor restriction (SMR) during development. To restrict movements, the feet of the pup were first tied together with medical tape and then attached to a cast made of epoxy stick 16 hr/day from P0/P1 to P28 (Fig. 3). The casts were well tolerated by the pups and mothers and allowed the pups to move at the hip, urinate, defecate and receive maternal care. The size of the casts was adapted to the growth of the rats [51–54]. Daily, while uncasted, the hind limb joints were passively moved by the investigators through their full range of motion. SMR induced a growth restriction during development up to P28 but not in adulthood [53,54].



### *Movement disorders*

We analysed the 3D kinematics of locomotion on a treadmill for a speed of  $0.23 \text{ m}\cdot\text{s}^{-1}$  at P30 and P65. Although cadence and stride duration did not differ, the length, amplitude and velocities of the foot were lower overall in SMR rats than controls, reductions that persisted over time. SMR induced significant knee and ankle overextension during automatic locomotion (Fig. 3), especially in the ankle in all gait phases examined, whereas the hip angle was unchanged. The maximal area of footprints of SMR rats was much smaller than that of control rats at P30 (Fig. 3). Control rats displayed a plantigrade locomotion [55], but SMR



rats appeared to develop locomotor and postural features that recapitulate “toe walking” or true pes equinus, which is among the most common symptoms seen in children with spastic CP [56] or ASD [57]. SMR rats exhibited reduced gait velocity and shorter stride lengths, also observed in people with spastic CP [58]. Footprint analysis showed a switch from plantigrade locomotion in controls to digitigrade locomotion during SMR, which suggested differences in tactile and proprioceptive inputs to the CNS during and beyond movement restriction. Taken together, these results emphasize the deleterious impact of disturbed proprioceptive feedback on the development and control of gait and posture.

In addition, the variations in most of the kinematics and joint angles decreased in control rats from P30 to P65, corresponding to typical gait plasticity in rats [23,32] or in humans [25]. In contrast, SMR led to increased variations in gait kinematic parameters but reduced joint angle variations; both persisting over time as compared with control rats. These results suggest differences both in the development and plasticity of locomotion over time and in the processing of somatosensory inputs [25,59] after SMR. Children with CP exhibited reduced repertoires of movements and behavioral strategies that match an overall reduction in gait variation [25,59]. However, high variation in cadence has been reported in children with CP, which leads invariably to delayed maturation of locomotion in older children with CP [58,59]. To a lesser extent than in CP, children with ASD also exhibited reduced postural stability and atypical gait, characterized by increased variations in stride length, posture and foot placement, reflecting impairments in the integration of somatosensory feedback [60].

Postnatal movement restriction and enduring locomotion disorders significantly altered joint, bone and muscle structure, but the passive range of motion of the hind limb joints was not affected during SMR. Tibial length and bone density appeared reduced, and the knee joint cartilage showed moderate degenerative changes in adult SMR rats (Fig. 3). Of note, SMR increased the weight load of the foot during weight support, but footprint area was reduced,

which suggests unbalanced muscle forces. SMR induced marked reductions in the width, circumference, length and cross-sectional area of the gastrocnemius, suggestive of muscle atrophy (Fig. 3). Comparable changes were observed in the rectus femoris and tibialis anterior muscles, indicating atrophy in several hind limb muscles after SMR. These results demonstrate that early atypical motor experience degraded muscle structure and motor outputs, with enduring effects into adulthood. More satellite cells in SMR than control muscles were indicative of increased regeneration or repair processes in the muscle [32] and a response to the myofiber atrophy or constraint-induced injury [32]. Hallmarks of fibrotic tissue after muscle injury, including increased production of collagen type I and connective tissue growth factor were found after a similar SMR procedure [52]. Although the gastrocnemius tendon length was not altered by SMR, the muscle atrophy and shortened tibial bone was correlated with the gait disturbances and corroborate the observations in children with spastic CP [61]. Thus, we consider that the joint abnormalities were secondary changes related to an imbalance in muscle forces across the joints due to both atrophied myofibers in the various muscles acting on the knee and ankle [32,39] and digitigrade locomotion after SMR. Such an enduring musculoskeletal histopathology likely contributed to the emergence, persistence or aggravation of the gait and posture disorders in a self-perpetuating cycle (Fig. 2C). In addition, we postulated that the enduring digitigrade locomotion, corresponding to equinus, was related to SMR because the experimenters were able to passively move the hind limb joints through their full range of motion, despite some resistance, during the daily uncaging period from P1 to P28 and after casting cessation during treadmill testing [53].

#### *Maladaptive plasticity*

To evaluate the possible presence of spasticity after SMR, reflected by hyperexcitability in the spinal circuitry, we assessed changes in the H-reflex [41]. In adult control rats, the H-

reflex was depressed by repeated nerve stimulation with increasing frequencies, corresponding to PAD. In contrast, PAD was reduced in adult SMR rats, which suggested signs of spasticity at 1 month after cessation of SMR. In the adult rat, 3 weeks of hind limb unloading increased the H-reflex gain [62]. Recently, botulinum toxin-related abolishment of sensory feedback and motor commands led to muscle atrophy and passive stiffness, maximal force reduction and increased stretch reflex in adult rats [63]. These studies combined emphasize the deleterious impact of abnormal somatosensory feedback on the emergence of signs of spasticity and spasms, muscle overactivity and related movement impairments.

Compared to control rats, adult SMR rats at 3 months after the end of SMR showed overall somatotopy and disrupted representation of contiguous skin surfaces of the foot S1 map. The total and glabrous somatosensory representation of the foot was reduced after SMR. Receptive fields (RFs) located on glabrous foot skin surfaces were about twice as large in SMR rats as in controls (Fig. 3), whereas the size of hairy-foot RFs did not differ significantly between the 2 groups, thereby confirming a specific impact of SMR on glabrous foot surfaces. This enlargement and more numerous multiple RFs led to overlapping glabrous RFs and less specific foot representations in SMR rats than controls, as denoted by orange cortical sectors (Fig. 3) pooling RFs encompassing 3 or more foot territories (i.e., toe or palmar pad). SMR increased the neural responsiveness to tactile stimulation, which indicates changes in neuronal properties and increased excitability in the somatosensory hind limb representation. Although the relative representation of each joint within the cortical motor map did not change in SMR rats, the total area for hind-limb motor maps was greatly reduced. In addition, the reduction of the minimal stimulation thresholds after SMR revealed an increase in motor excitability.

Furthermore, the extracellular concentration of glutamate was greater in SMR rats than in controls, but the extracellular concentration of GABA did not differ after SMR by using *in vivo* microdialysis. The amount of vGLUT1 increased about 90% in SMR rats and that of

vGAT did not differ, which suggests a cortical hyperexcitability in the sensorimotor cortex after SMR (Fig. 3). No evidence of histopathology was observed in the somatosensory, motor and cingular cortices or underlying white matter, including in the corpus callosum of any SMR rat as compared with control rats. In addition, there were no signs of axonal degeneration, astrogliosis or neuroinflammation in the brains or spinal cords of control and SMR animals. The numerical density of neurons and GABAergic interneurons did not differ between SMR and control rats in either the S1 or M1 cortex. Thus, SMR appeared to have no significant impact on brain neuroanatomy, as compared with controls but only on functional organization.

Preliminary data showed that SMR delays the emergence of sensorimotor reflexes, such as negative geotaxis, cliff avoidance, and surface righting reflex; induces hyperactivity and over-exploration of objects; and impairs integration of sensory information and working memory in object recognition memory tasks. It also seems to impair some executive functions in the elevated plus maze and social interactions tasks (unpublished data). Thus, in the absence of brain damage, the long-lasting locomotor disorders, hind-limb musculoskeletal histopathology, hyperreflexia and functional disorganization of the adult sensorimotor cortex, as well as signs of hyperactivity, executive dysfunctions and impairments in short-term memory, recapitulate several symptoms and neurological features observed in people with ASD and DCD in general [12,13,17,18,26,54,64]

*Putative interactions and processes underlying maladaptive plasticity related to SMR*

We postulate that early limited and abnormal patterns of movements during SMR provide atypical sensorimotor experience at the origin of adult locomotor disorders (e.g., digitigrade gait), increased stretch reflex (i.e., lumbar spinal cord hyperexcitability, spasticity, spasms, contractures etc.) and musculoskeletal tissue degeneration (Fig. 2C) as compared with typical

sensorimotor development in controls (Fig. 2A). Our results suggest the existence of a self-perpetuating cycle, in which musculoskeletal pathologies likely contribute to muscle overactivity and locomotor disorders. Spasticity and related muscle disorders may in turn contribute to enhanced musculoskeletal and locomotion disturbances (Fig. 2C). As a consequence, degraded movements due to spastic muscles and digitigrade locomotion likely produce atypical somatosensory feedback to the immature sensorimotor circuitry, including the lumbar spinal circuitry involved in automatic gait, and primary somatosensory and motor cortices associated with other subcortical structures in the sensorimotor loop [65]. In the absence of brain damage, this atypical somatosensory reafference probably triggers and maintains the functional disorganization of both the somatosensory and motor cortical maps and lumbar spinal cord, involved in both motor commands during automatic locomotion and the emergence of muscle overactivity and paresis (Fig. 2C; [59,66]). The functional disorganization of the sensorimotor circuitry may in turn produce atypical or aberrant motor commands, such as abnormal muscle synergies involved in gait disorders observed in immobilized patients with stroke [67,68]. Thus, we propose the existence of 3 interplaying, self-perpetuating cycles: the first is related to peripheral changes, including gait disorders, increased stretch reflex and musculoskeletal pathologies (Fig. 2C); the second involves the sensorimotor circuitry; and the third corresponds to interactions between the peripheral and central circuitry that are interconnected by the somatosensory reafference (altered by abnormal movements) and atypical motor commands that drive abnormal movements (Fig. 2C). The movement disorders and maladaptive reorganization in the lumbar spine, somatosensory and motor cortices observed after early SMR appear to recapitulate several symptoms and neurological features found in people with CP, ASD, and DCD in general [12,17,26,58,69].

## **Conclusion**

Children with CP or DCD share early aberrant sensorimotor experiences resulting from atypical spontaneous or general movements [23,24,69] and exhibit neuroanatomical and/or functional disorganization, especially inabilities in processing and integrating sensory information [20,69,70]. In addition, general movements are predictive of neural, motor and cognitive outcomes in children with CP and DCD [12,22,24,26,69]. Thus, our animal studies MIUH and postnatal SMR support the idea that developmental maladaptive plasticity may lead to long-lasting disturbances of motor outputs, as observed in CP and DCD, and point out the pertinence of early rehabilitative programs, such as the Care Toy System [71] or HABIT-ILE [72]. According to the self-perpetuating cycles and putative mechanisms described above, we strongly believe that rehabilitation needs to focus on physical and cognitive training leading to adaptive brain plasticity and improve the physical body situation, because both appear to continuously interplay. In case of perinatal brain damage, we consider that early therapy based on mesenchymal stem cells may reduce early neuroinflammation and thus diffuse brain lesions and subsequently alleviate or prevent the emergence of neurodevelopmental disorders [73]. Strong efforts are still required to assess short- and long-term effects and consequences of stem-cell therapy on body and brain reorganization.

## **Figure legends**

Figure 1. Schematic summary of the diversity of symptoms that successfully reproduces our rat model of encephalopathy of prematurity, based on mild intrauterine hypoperfusion (MIUH) at embryonic day 17 (E17). See “Animal model of cerebral palsy” for details. WMI, white matter injury; S1, primary somatosensory cortex

Figure 2. Illustration of the putative interactions and processes underlying the emergence of movement disorders and brain plasticity. A) Schematic representation of the putative interactions between the different variables assessed (locomotion, musculoskeletal tissues, Hoffman-reflex, somatosensory and motor representations of the hind limb and excitation-inhibition neurotransmission in the sensorimotor cortex) that may occur during typical sensorimotor development in control rats. Daily activities provide early typical sensorimotor experience that allow muscle synergies and typical gait to interplay harmoniously. Normal movements during typical gait produce typical sensorimotor feedback to the immature brain, contributing to the development and refinement of connections, maps and functions (e.g., normal motor command to muscles that in turn contribute to muscle synergies and typical movements in a virtuous self-perpetuating cycle). Excitation–inhibition balance also participates in the refinement of neural maps and connections. S1, primary somatosensory cortex; M1, motor cortex. B) Schematic illustration of the detrimental impact of mild intrauterine hypoperfusion (MIUH) on neuromuscular interplay and brain disorganization. MIUH induces early inflammation and likely enhances immunoreactions that lead to diffuse WMI (loss of oligodendrocyte precursors) and neuronal loss in the developing central nervous system (CNS). Such a diffuse CNS damage leads to decreased levels/expression of ubiquitous KCC2, a K-Cl cotransporter that regulates chloride homeostasis and cell excitability from spine to brain. Such a decrease leads to lumbar spine hyperexcitability and the emergence of spasticity and muscular spasms in MIUH rats, as shown by reduced post-activation depression (PAD). In addition to reduced density of neurons, WMI below the S1 cortex interferes with typical integration of somatosensory inputs/reafference, leading to the functional disorganization of S1. Although the M1 cortex is not altered after MIUH, mild musculoskeletal degradation, locomotor impairments and signs of spasticity are observed in MIUH, and appear to interplay in a detrimental self-perpetuating cycle. Does the sensorimotor

circuitry disorganization also have an impact on brain neuroanatomy and functions, as observed after MIUH? How inflammation, WMI, KCC2 reduction and other factors after MIUH contribute to the brain disorganization is still an open question. C) Schematic illustration of the deleterious impact of postnatal sensorimotor restriction (SMR) on neuromuscular interplay. Movement restriction during postnatal hind limb immobilization provides early atypical sensorimotor experience that leads to gait disorders, musculoskeletal pathologies and hyperreflexia, as signs of spasticity. In turn, gait disorders and spastic muscles provide atypical somatosensory feedback/reafference to the immature sensorimotor circuitry, mainly the spinal network and the primary S1 and M1 cortices that intercommunicate. Such atypical somatosensory feedback likely degrades the functional organization of the somatosensory and motor maps and spinal network, thus producing abnormal motor commands that finally aggravate gait disorders, spasticity and musculoskeletal abnormalities into interrelated self-perpetuating cycles. Excitation–inhibition imbalances that tip the balance to hyperexcitability in sensorimotor hind limb cortices have more impact on the reorganization of somatosensory maps than on motor maps. Hyperexcitability in the lumbar spinal cord was previously shown as an enduring hyperreflexia in adult SMR rats. KCC2, K<sup>+</sup>-Cl<sup>-</sup> cotransporter 2; PAD, post-activation depression or rate-dependent depression.

Figure 3. Schematic summary of the variety of symptoms reproduced in our rat model of developmental coordination disorder based on early movement restriction. Such a hind-limb immobilization from birth to 1 month provides atypical sensorimotor experience during development. See text in “Animal model of developmental coordination disorder” for details. SMR, sensorimotor restriction



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