In: Movement Disorders: Causes, Diagnoses and Treatments ISBN 978-1-61209-200-3
Editors: Barbara J. Larsen, pp.

Chapter 2

Peripheral and Central Changes Combined Induce Movement Disorders on the Basis of Disuse or Overuse

Jacques-Olivier Coq[1] and Mary F Barbe[2]
[1]UMR 6149 Neurobiologie Intégrative et Adaptative, CNRS/Aix-Marseille Université, Marseille, France
[2]Department of Anatomy and Cell Biology, Temple University, Philadelphia, USA

Abstract

To gain new insights into the underpinning mechanisms of movement disorders observed with both cerebral palsy and repetitive motion disorders, we have investigated the long-term effects of movement disuse or overuse on musculoskeletal tissues and topographical organization of the primary somatosensory and primary motor cortices, using two different rat models. We provide strong evidence that experience-dependent movements play a crucial role in shaping normal as well as aberrant movement abilities. Cerebral palsy is a developmental neurological disorder characterized by spasticity of some muscles, but also disuse in other muscles, and motor abnormalities. Our data from a rat model of cerebral palsy shows that aberrant sensorimotor inputs during development resulting from prolonged disuse (i.e. hind limb immobilization during the first month of life) induces peripheral tissue changes, such as muscle atrophy and extracellular matrix changes, joint degeneration, and drastic topographical disorganization of primary somatosensory and motor cortical hind limb representations. These peripheral and central tissue changes were associated with increased muscular tone at rest and with active flexion and extension around movement-restricted joints that resulted in abnormal walking patterns. Observed tissue changes and movement disorders were worsened when

[1] Email: jacques-olivier.coq@univ-provence.fr, UMR6149 Neurobiologie Intégrative et Adaptative, CNRS/Aix-Marseille Université, Pôle 3C, Case B, 3 Place Victor Hugo, 13331, Marseille Cedex 03, France. Tel: +33 413 55 08 63, Fax: +33 413 55 08 69.

2 Email: mary.barbe@temple.edu. Department of Anatomy and Cell Biology, Temple University, 3500 North Broad Street, Philadelphia, PA 19140, USA,Tel: +1 215/707-6422 fax: +1 215/738-2966.

developmental disuse was combined with neonatal asphyxia. In contrast, repetitive motion disorders, such as carpal tunnel syndrome and focal hand dystonia, are a type of overuse associated with tasks that require prolonged, repetitive behaviors. Our data from a rat model of repetitive reaching and grasping shows that peripheral tissue changes are induced with cumulative task exposure, including myofiber fray, fibrotic nerve compression, and increased macrophages and inflammatory cytokines. These tissue changes were associated with declines in reach performance, grip strength and agility. The motor declines also correlated with disorganization of the forepaw representation in the primary somatosensory cortex, including the emergence of large receptive fields, and a drastic enlargement of the overall forepaw map area of the primary motor cortex, in which emerged the representation of joint movements specifically involved in the repetitive task. Peripheral inflammation correlated with signs of central sensitization (mechanical allodynia, myalgia, and increased neurochemicals and cytokines in the spinal cord), and with the reduced amount of current needed in the motor cortex to evoke forelimb movements. Our data from a rat model of repetitive motion injuries show that peripheral inflammation, spinal cord neuroplasticity and cortical neuroplasticity jointly contribute to the development of chronic repetitive motion disorders. In conclusion, both prolonged disuse and overuse lead to both peripheral and central changes that are interdependent to drive cerebral plasticity and altered motor output function.

Introduction

The changes in skeletal muscle physiology, gait, posture and brain adaptation to microgravity exposure has been a medical and physiological concern since the early 1960 and the human flight in space (more than 500 human beings have flown into space since 1961; Narici and De Boer, 2010). Many studies in animals and humans have been devoted to investigate peripheral and central changes in presumed models of disuse, such as spaceflight, bed rest, hind limb immobilization or suspension, tetrodotoxin (TTX), spinal cord transection or denervation, which are actually models of normal or decreased use, but appear to be interesting models of abnormal inputs to the brain. For instance, early sensory input deprivation has been shown to impact the development of brain cortical function and structure.

An other line of work on disuse have been dedicated to study the impact of spontaneous movements on the development of gait, posture and adaptive motor behavior in both normal infants and children with cerebral palsy (Hadders-Algra, 2001, 2004, 2007, 2008; Heineman et al., 2010). Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances occurring in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, by epilepsy and secondary musculoskeletal problems (Rosenbaum et al., 2007; Pakula et al., 2009). Normal infants produce a large and rich repertoire of spontaneous movements from early fetal life until the end of the first half of a year of life. In contrast, children with CP display scarce, monotonous and stereotypical patterns of cramped-synchronized spontaneous movements that lack complexity, variation, and fluency (Prechtl, 1997; Hadders-Algra, 2004; Einspieler and Prechtl, 2005; Hadders-Algra et al., 2010). Deficits in these spontaneous movements could account for musculoskeletal tissue changes found in these children. Indeed, varying degrees of atrophy and hypertrophy of muscle fibers

(Lindboe and Platou, 1982; Romanini et al., 1989; Rose et al., 1994; Marbini et al., 2002) and increased fat and connective tissue within muscles (Castle et al., 1979; Järvinen et al., 2002) have been reported in children with spastic CP. These muscle changes could be responsible for abnormal forces on bones and joints resulting in secondary bone malformations (Banks, 1972; Gormley, 2001) and/or articular cartilage degenerative changes (Banks, 1972; Lundy et al., 1998). In previous studies, we hypothesized that peripheral changes have a deleterious impact on brain structure, physiology and function following abnormal inputs during development (Strata et al., 2004; Coq et al., 2008). Indeed, recent studies in humans have provided evidence of maladaptive somatosensory and cortex reorganization and of impairments in tactile and kinesthesic discrimination abilities in patients with CP (Clayton et al., 2003; Gordon et al., 2006; Hadders-Algra and Gramsbergen, 2007; Hadders-Algra, 2008; Burton et al., 2008, 2009; Wingert et al., 2008, 2009, 2010; Andiman et al., 2010).

In contrast to the above disuse model, several types of overuse injuries are associated with performance of tasks that require prolonged, repetitive behaviors. These disorders are also known as repetitive motion injuries (RMIs) and musculoskeletal disorders (MSDs), and include peripheral neuropathies (e.g. carpal tunnel syndrome), tendinitis, tendinopathies, myalgias, myopathies and stress fractures (Forwood and Parker, 1991; Fredericson et al., 1995; Ljung et al., 1999; Larsson et al., 2000; Freeland et al., 2002; Luime et al., 2004; Keir and Rempel, 2005; Szabo et al., 2006; see Barr et al., 2004 for further review). Focal hand dystonias can also develop in patients with performance of repetitive tasks, although they are thought to be the consequence of central nervous system changes rather than peripheral tissue changes (Byl et al., 2000; Byl, 2009).

Overuse injuries of the upper extremity are painful, potentially disabling and costly. Work-related overuse injuries accounted for 30% of lost workday injuries and illnesses in US industry in 2006 (Bureau of Labor Statistics, 2007). Upper extremity overuse injuries have a high impact on lost workdays and cause substantial worker discomfort, disability and loss of productivity. For example, carpal tunnel syndrome and repetitive motion tasks (e.g. grasping tools) resulted in the longest work absences, with a median of 27 and 19 lost workdays, respectively. The most common musculoskeletal disorder in a study by Gerr et al. (2002) was somatic pain syndrome. Patients with upper extremity overuse injuries have increased frequency of local pain and tenderness, peripheral nerve irritation, weakness and increased frequency of symptoms such as pain and tenderness at multiple anatomical sites (Carp et al., 2007). In this last study, patient symptoms interestingly correlated with increased serum inflammatory cytokines (Carp et al, 2007).

However, in spite of numerous epidemiological studies demonstrating a positive relationship between exposure to repetitive and/or forceful motion and the prevalence of overuse injuries (Bernard, 1997), the mechanisms of pathophysiology are incompletely understood. In part, this is due to ethical constraints in obtaining tissue biopsies from healthy working populations in order to study the natural history of these disorders. Also, if there is a surgical intervention, the initiating injury stimulus is often long since past. It is thus hard to conclude which biochemical changes cause or follow the physiological mechanisms leading to a patient's clinical presentation. Animal models provide an opportunity to examine such tissue effects at a much earlier time point and under experimental conditions in which exposure can be controlled.

To gain new insights into the underlying mechanisms of movement disorders, we have investigated the long-term effects of movement disuse or overuse on musculoskeletal tissues

and topographical organization of the primary somatosensory and motor cortices. We provide evidence that experience-dependent movements, through physiological mechanisms of plasticity, play a crucial role in building normal or abnormal motor capabilities during development and in adulthood.

I. Disuse During Development

1. Our Animal Model of Sensorimotor Disuse

We utilized hind limb immobilization during development as a means to produce limited and abnormal patterns of movements during maturation. We hypothesized that repetitive, reduced and abnormal movement would provide abnormal sensorimotor feedback to the primary somatosensory (S1) and motor (M1) cortices that would lead to S1 and M1 deleterious reorganization. We also hypothesized that prolonged limb disuse would also induce deleterious changes in musculoskeletal tissues, which in turn would contribute to aberrant sensory inputs to the immature brain. The S1 and M1 deleterious reorganization in combination with hind limb tissue degradation should then result in degraded motor function.

Sprague-Dawley rat pups from different litters were pseudo-randomly assigned to several experimental groups, one of which was hind limb immobilization from P1 to P28. A detailed description of the restriction procedures has been previously published (Strata et al., 2004; Coq et al., 2007, 2008; Delcour et al., 2009). Pups were restrained for 16 hours per day from P1 or P2 to P28. The feet of the pups were first gently bound together with medical tape. The feet were not taped so tight as to cause anoxia (changes in color) in peripheral tissues. The hind limbs were then immobilized in an extended position by firmly taping them to a cast (Figure 1), which allowed only limited movements around the hip joint. The cast made of hand-moldable epoxy putty stick was well tolerated by pups and mothers, and allowed the pups to urinate, defecate and to receive maternal cares necessary for good health conditions. After casting, pups were returned to their mother and unrestrained littermates. The restrained rats were allowed to move freely for 8 hours per day as the epoxy casts were removed for that period of time per day. The size of the casts was adapted to the growth of the rats from P1 to P28. We observed that body growth of restrained pups was significantly lower than that of unrestricted littermates (see Strata et al. 2004 for details). However, the differences in body growth between restricted and unrestrained rats decreased over time after the cessation of sensorimotor restriction (Strata et al., 2004).

2. Motor Outputs Affected by Disuse: Open-Field Exploration, Locomotion and Motor Skills

A. Open-Field Activity

To our knowledge, no studies dealing with hind limb unloading have been devoted to open-field measurements.

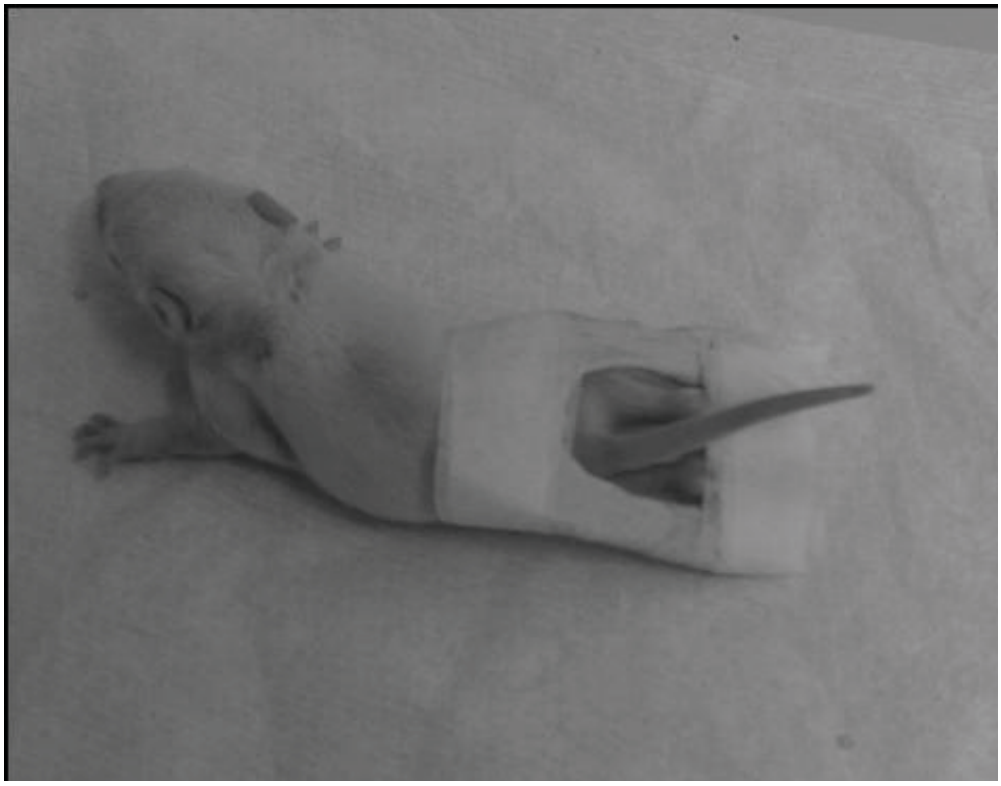

Figure 1. Young rat experiencing sensorimotor restriction (SMR). The feet of the pup were first tied together with medical tape and then were firmly attached to a cast made of epoxy stick. The proximal part of the hind limbs was also taped to the cast. The sensorimotor restriction lasted for 16 hours a day every day from P1 to P28. The casting was well tolerated by pups and mothers.

We examined spontaneous exploratory and locomotor activity of the rats by counting the number of square (10 x 10 cm) crossings, rearings, defecations and cleanings during 10 min in an empty arena. Sensorimotor-restrained (SMR) rats displayed fewer square crossings, rearings and cleanings than control rats (Coq et al., 2007).

B. Posture and Gait

We also explored posture and gait changes in order to assess gross motor function. Qualitative observation revealed that SMR rats exhibited irregular step cycles, difficulty in coordination between homolateral (fore vs. hind) limbs, elevated hindquarters, externally rotated feet, widened support base and some rats dragged their feet and/or toes behind, so the forelimbs propelled them (Strata et al., 2004).

Gait was also assessed via treadmill walking. Using a treadmill speed of 0.23 $m.s^{-1}$, preliminary data (Coq et al., 2007) on SMR rats at P30 showed that they displayed hind limb hyperextension, which was characterized by larger knee and ankle angles at the beginning of the stance (toe-contact on the belt) and swing (toe-off), and at the maximal height of the swing than control rats, while the angle of hip was comparable in each phase. While gait was degraded in restrained rats, with multiple drifting on the treadmill and little hopping capacity, the number of steps per second performed by SMR was similar to that performed by controls. The length of the swing was also shorter in SMR rats while duration was greater and the

height of the swing was shorter (Coq et al., 2007). In a study from a different laboratory using the same procedure and duration of hind limb immobilization as ours, Marcuzzo et al. (2008) also found an elevation of the hindquarters during posture and walking, which was caused by abnormal extension of both ankle and knee joints. They also showed a decrease in the stride length and wider foot angle at toe-contact, suggesting greater foot rigidity. In addition, their SMR rats underwent treadmill training once a day for 3 weeks, an intervention that improved stride length, but not the foot angle (Marcuzzo et al., 2008).

Hind limb unloading (HU) in adulthood has provided interesting data on the effects of disuse on gait and posture. Canu et al. (2005) showed that HU rats exhibited increased stride length during treadmill locomotion, hyperextensions at the end of the stance, and a decrease in ankle angle during the remaining part of the stride compared to controls. The ankle remained overflexed from paw contact to the end of midstance, whereas ankle extension increased during push-off. During this overextension, rats appeared to walk on their toes although soleus muscle (ankle extensor) activity was not altered in HU rats (Canu et al., 2005). In addition, HU slightly altered the patterns of neuromuscular activation during treadmill locomotion, suggesting alterations of peripheral afferent information that regulates gait (Canu and Falempin, 1997, 1998). In fictive rhythmic motor episodes elicited by electrical stimulation of the mesencephalic locomotor area, the overall motor pattern was not affected by HU, but extensor muscle nerves were frequently activated and their burst duration were increased relative to control rats (Canu et al., 2001). Consistent with SMR and HU, a 9-day space flight induced overextension of the knee and ankle in rats during both stance and swing phases(Walton, 1998). In addition, it appears that a postnatal critical period (from P14 to P30) exists for the development and maturation of some movement patterns, such as surface righting (Walton et al., 2005).

C. Motor Skill Development

More challenging situations than treadmill locomotion, such as walking on a narrow suspended bar (beam), ladder or rotarod, may allow one to detect additional deficits and to differentiate the involvement of spinal and supraspinal structures in locomotion (Beloozerova et al., 2003; Drew et al., 2008; Garnier et al., 2008). Our SMR rats were barely able to stay on the beam at P17, they often hung on the bar before falling off, and then gradually but slowly improved over time relative to controls (Strata et al., 2004). Using the same SMR methods, Marcuzzo et al. (2008) found comparable results with beam walking.

Our SMR rats spent much less time than controls on the rotarod, and propelled their body using the forelimb rather than the hind limbs, along with their belly in contact with the rotarod (Strata et al., 2004).

Using the ladder walking, Marcuzzo et al. (2008) showed that SMR rats made more stepping errors than controls with increasing numbers of errors over time. These authors also found that SMR delayed stability on an inclined plane (negative geotaxis) but accelerated the appearance of the proprioceptive placing reflex. During ladder walking, HU rats exhibited enhanced duration of step, stance and swing phases, increased ankle flexion during stance, hyperextension at the beginning of the swing (toe-off), and lower protraction during swing, with increased flexor and extensor burst duration in this challenging gait situation (Canu and Garnier, 2009).

3. Peripheral Musculoskeletal Changes Induced by Disuse

Limb disuse can alter physiology and function of muscles and joints as well as bone structure mainly through degenerative processes, as explained further below.

A. Muscle Changes

Disuse resulted in decreased individual myofiber diameters of the triceps surae muscle, a knee and ankle plantar flexor, whereas the myofiber diameters of the quadriceps muscle and the hamstrings, a knee extensor and a knee flexor, respectively, were unchanged (Coq et al., 2008). We used bin frequency counts of myofiber diameters and found that the triceps surae of SMR rats exhibited greater numbers of myofibers with diameters ≤ 10 μm than controls and a loss of all myofibers with diameters over 60 μm. According to (Johnson and Kucukyalcin, 1978), myofiber diameters smaller than 10 μm represent an index of myofiber atrophy. These results are similar to those of Marcuzzo et al.'s (2008), in which they observed smaller myofiber areas in the soleus muscle, a foot plantar flexor, in SMR rats than in controls. They also observed a higher percentage of atrophied fibers (0-500 μm), with more rounded profile, and thus increased fiber density, as a consequence of the reduction in the mean fiber area. In their study, treadmill training for 3 weeks after restriction increased the myofiber area and decreased the percentage of atrophied fibers of the soleus (Marcuzzo et al., 2008).

It is now well admitted that hind limb unloading (HU), used as a chronic weightless bearing and movement disuse, have long lasting effects on muscle physiology and function, as well as denervation, tenotomy, spaceflight in both rats and humans or bed rest in the latter (see Booth, 1982; Talmadge et al., 1995; Ohira et al., 2002a; Narici and de Boer, 2010). Briefly, HU induces i) myofiber atrophy (i.e. a reduction in cross-sectional area), especially in predominant slow extensor muscles while fast muscles are almost unaffected (Booth, 1982; Stevens et al., 1990; Ohira et al., 2002b; Kawano et al., 2002; Deschenes et al., 2003; Vermaelen et al., 2005; Wang et al., 2006; Fujita et al., 2009; Schuenke et al., 2009; Narici and de Boer, 2010), ii) changes in fiber phenotypes, such as increases in the expression of fast myosin heavy chains in normally slow muscles (Talmadge et al., 1995; De-Doncker et al., 2002; Kawano et al., 2002; Ohira et al., 2002a; Stevens et al., 2004; Giger et al., 2005, 2009; Yu et al., 2007; Narici and de Boer, 2010; see however Schuenke et al., 2009), iii) drastic reductions of EMG activity of muscles in immobilized limbs and neural drive (Booth, 1982; Ohira et al., 2002a; Westerga and Gramsbergen, 1993; Leterme and Falempin, 1998; Narici and de Boer, 2010), and iv) decreases in muscle glucose consumption and contraction dynamic performance, such as muscle strength, force and power (Booth, 1982; Shenkman et al., 2002; Stein et al., 2002; Stevenson et al., 2003; Kourtidou-Papadeli et al., 2004; Narici and de Boer, 2010).

In our study on disuse, muscle atrophy was accompanied by intramuscular connective tissue changes in all hind limb muscles (Coq et al., 2008). Collagen type I showed a small increase in SMR rats, but connective tissue growth factor (CTGF) increased significantly after restriction compared to controls. CTGF is a cytokine and growth factor that induces fibroblast proliferation and matrix production, and it correlates with fibrotic tissue disorders (Hayashi et al., 2002). Many of the CTGF immunoreactive cells were small cells surrounding the myofibers in the perimysium and endomysium (Coq et al., 2008; Figure 2A,B).

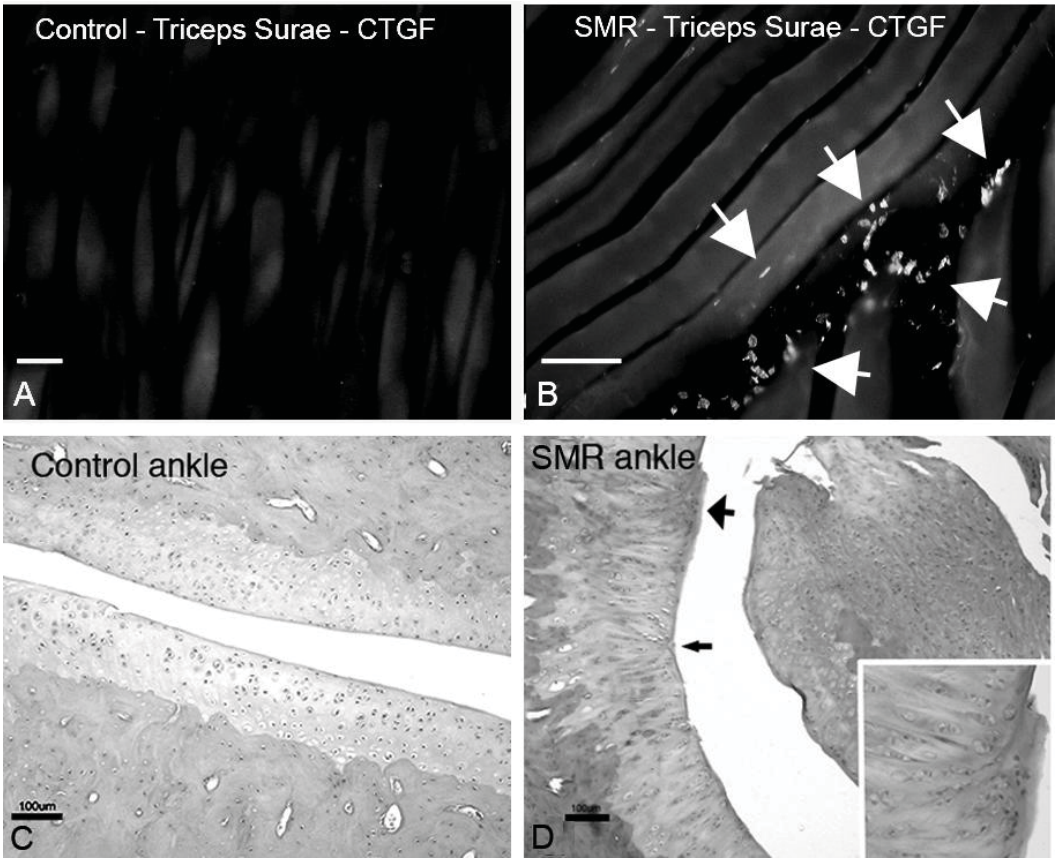

Figure 2. Muscle and ankle histopathlogy in control and sensorimotor restricted (SMR) rats. A-B) Photomicrographs showing connective tissue growth factor (CTGF) immunoreactivity in hind limb muscles from a control rat and a SMR rat. Specifically, longitudinal sections of the triceps surae muscle, also known as gastrocnemius and soleus, are shown. A) Control muscle shows no CTGF immunostaining. B) SMR muscle shows increased CTGF-positive cells that appear to be fibroblasts by location (between muscle fibers primarily), size, and CTGF production. The myofibers themselves also have a low level increase of CTGF within their cytoplasm. Scale bars are 50 μm. C-D) Photos of ankle joints from control and SMR rats. C) Control joint showing healthy articular cartilage. D) SMR joint showing eburnations (small arrow) in the superficial cartilage layers, tidemark changes between the bone and cartilage, and fibrotic cartilage (large arrow). Inset shows a higher power of fibrotic area. Hematoxylin and eosin staining. Scale bars correspond to 100 μm. Figure modified with permission from Coq et al. (2008).

Marcuzzo et al. (2008) also found significant increases in interstitial connective tissue, in their case in the soleus muscle of SMR rats. In that study, treadmill training attenuated the increase in connective tissue and also led to increased polygonal myofibers, instead of rounded fibers. As in SMR, HU also increased connective tissue and satellite cells in muscles (Wang et al., 2006; Kawano et al., 2008; Heinemeier et al., 2009). In regard to disuse-induced changes in muscle force and tension, HU decreased tendon stiffness, especially Achilles tendon, so that the extensibility of tendons increased to compensate some muscle changes (Heinemeier et al., 2009; Narici and de Boer, 2010). Proprioceptive information from muscle afferent fibers is crucial in contraction force regulation and HU has been showed to decrease

the dynamic peak but to increase the static sensitivity of Ib afferent fibers (Treffort et al., 2005).

B. Alterations of Joints and Bones

Lastly, we observed articular cartilage degradation in the hind limbs as a result of disuse (Figure 2C,D). For example, medial menisci in the knee joints of SMR rats were undergoing the initial stages of calcification, changes not observed in control rats. The knee articular cartilage was only mildly affected after SMR, with increased condensations in upper cartilage layers in 50% of the rats, but no signs of eburnation or thinning. In contrast, articular cartilages of ankle joints of 62% of the SMR rats showed eburnations, tidemark changes, and fibrocartilage degenerative changes. These degenerative cartilage thickenings were immunoreactive for CTGF, indicative of fibrotic cartilage formation, a type of cartilage degeneration (Coq et al., 2008). The hip joint was not studied in these animals, although in several of the SMR rats, femoral internal rotation was observed (unpublished data), a finding reminiscent of femoral anteversion in children with cerebral palsy. In the same line, HU appears to weaken bone and cartilage structures, in relation to enhanced apoptosis of osteocytes and chondrocytes (Basso and Heersche, 2006; David et al., 2006; Pan et al., 2008; Shimano and Volpon, 2009). As a general physiological adaptation, HU increases sympathetic but reduces parasympathetic cardiac tone, and also induces anhedonia (Moffitt et al., 2008).

4. Central Changes Related to Disuse

To our knowledge, there are no studies dealing with the effects of disuse, such as SMR or HU, on spinal central pattern generators and other subcortical structures, whereas many studies have been devoted to cortical areas.

A. Map Reorganization in the Primary Somatosensory Cortex (S1)

Electrophysiological S1 maps of the hind limb skin representation were recorded in layer IIIb-IV and were located between -1 and +3 mm from bregma in the rostrocaudal axis and between 1 and 4 mm in the mediolateral direction and often overlapped with the M1 layer V representation of hind limb movements (see also Donoghue, 1995). Despite idiosyncratic differences, the S1 hind limb representation in controls presented common somatotopic features (Coq et al., 2008). The hind paw representation was usually located medial to the forepaw map and rostral to the tail and back/ventrum representations. From rostral to caudal, cortical sites progressed from the toes, plantar pads of the sole to the heel and leg. From lateral to medial in the rostral portion of the hind paw map, the toes were topographically represented from toe 1 (t1) to toe 5 (t5) (Figure 3A). The hairy representation of the toes was generally located medially (t1 to t3, innervated by the saphenous nerve) and laterally (t3 to t5, innervated by the sciatic nerve) to the glabrous representation of the toes (innervated by the sciatic nerve).

The overall somatotopy of the foot maps was preserved in our SMR rats in which the representation of contiguous skin surfaces of the foot was partially disrupted (Figure 3B).

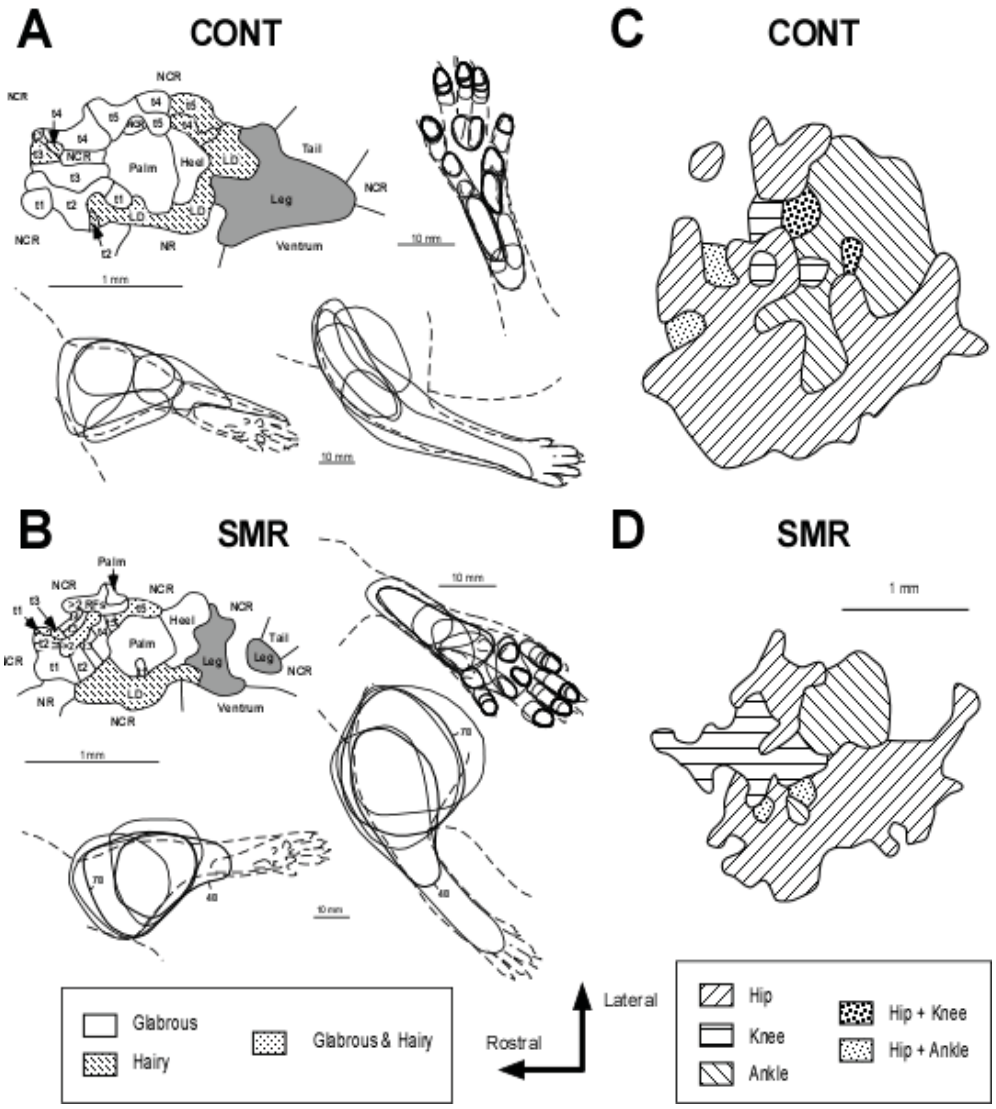

Figure 3. Effects of sensorimotor restriction (SMR) during development on the topographical organization of the hind limb maps in the primary somatosensory (S1) and motor (M1) cortices. A-B) Illustration of the S1 representation of the hind paw and receptive fields (RFs) located on the glabrous foot skin and leg. A) Example of the S1 hind limb map and RFs in a representative control rat (CONT). B) Representative S1 map and RFs of the hind limb in a rat that experienced developmental SMR. Relative to controls the organization of the S1 foot map was degraded in SMR rats and RFs were enlarged. More multiple RFs were recorded in SMR rats. In addition, we found the emergence of RFs that encompassed the two sides of the leg in SMR rats (RFs # 48 and #78), while none in CONT animals. C-D) Illustration of the movement representation of the hind limb joints in M1. C) Representative M1 hind limb map in a control rat (CONT). Note the absence of precise topographical organization of the movements of the joints. D) Developmental SMR induced a reduction in the overall size of the M1 hind limb maps while the relative areas devoted to the different joint representations were not significantly altered. Abbreviations: LD, large dorsum of hind paw; NCR, non cutaneous responses; NR, no response; t1-t5, toe1 to toe 5; >2 and >2 RFs, cortical zones whose RFs encompassed more than 2 distinct hind paw subdivision, i.e. toe or plantar pad. Figure modified with permission from Coq et al. (2007, 2008).

The total S1 area devoted to the foot representation was not statistically different from controls, but the proportions of cortical sites responding to both hind paw cutaneous stimulation and nail movements were about twice in SMR than in control rats (Coq et al., 2008). These results show a change in neuronal selectivity between cutaneous and nail movement inputs and emphasize the sensorimotor restriction-induced alterations of the S1 neuronal properties. Using the same SMR procedures, (Marcuzzo et al., 2010) found a reduction in neuronal counts in the layer V of S1 while the number of glial cells increased, suggesting gliosis and pathological conditions often related to stroke.

The proportions of cortical sites with at least three disjunctive, multiple receptive fields (RFs) were more than 10 times greater in SMR rats than in controls, while the percentages of disjunctive, double RFs did not differ between both groups. As the numbers of multiple RFs increased with disuse the RF size also increased (Figure 3B). The sizes of all RFs were about twice as large in SMR as in controls. This enlargement led to a greater overlap between glabrous RFs, a coarser-grained representation of these surfaces and patchy representations of glabrous and hairy foot surfaces after SMR. To better understand the topographic disruption of the S1 foot maps, the proportions of RFs that encompass both glabrous and hairy foot surfaces were greater in SMR. As a consequence of larger and overlapping RFs, and numerous multiple RFs located on both sides of the foot, the delineation of toe and pad representation borders was difficult in our SMR rats, so that penetrations with at least three multiple RFs were pooled together in specific cortical sectors of the foot maps (Figure 3B).

The proportions of RFs covering both sides of the leg were also greater after SMR since no such double-sided RFs were present in the control rats. The presence of abnormally large RFs covering both sides of either the foot or leg in restrained rats (Coq et al. 2007, 2008) seems in accordance with the level of spasticity reported in our previous studies. Indeed, Strata et al. (2004) reported that restrained rats displayed hind limb rigidity and hypertonicity, as well as increased velocity-dependent resistance to passive motion in all joints of the hind limbs, sign of disabling levels of spasticity, as defined by (Lance and McLeod, 1981). Co-contractions of antagonist muscles of the leg may have induced synchronous activations of cutaneous mechanoreceptors, thus leading to very large RFs covering the entire leg by physiological mechanisms of plasticity (e.g. Wang et al., 1995; Byl et al., 1996, 1997). In the same line, hypertonicity and rigidity of toes and other joints found in SMR rats (Strata et al., 2004) may have contributed to the increase in S1 nail movement representation and to the decrease in neuronal selectivity to afferent inputs in S1 (Coq et al., 2008).

Thus, disuse induced the emergence of RFs located on both sides of the leg, as well as RFs on both glabrous and hairy sides of the foot. In addition, SMR also increased the cortical responsiveness to tactile stimulation. And disuse during development induced a topographical degradation of the S1 foot maps and alterations of the neuronal properties (Coq et al., 2008). Interestingly, Canu et al. recently found changes in cortical neuron properties, such as decreased intrinsic excitability (reduction in input membrane resistance and slow after hyperpolarization, increased rheobase, but unchanged resting membrane potential) of cortical cells in layer II to VI of the sensorimotor cortex in adult rats that experienced 2 weeks of HU (Canu et al., 2010).

Previous studies based on disuse during adulthood partially confirm our results. Forepaw immobilization with a plaster cast for one or two weeks degraded the S1 topographic organization and drastically reduced the contralateral S1 map area, while the size of the corresponding RFs was unchanged (Coq and Xerri, 1999). Two weeks of HU also reduced the

S1 map but increased the proportion of large foot RFs (Langlet et al., 1999a, 1999b) and induced abnormal locomotor patterns, such as hind limb hyperextension (Canu and Falempin, 1996). However, we cannot rule out possible effects of restraint-induced stress on S1 map reorganization (Canu et al., 2007), but we previously reported no increase in stress induced by forepaw immobilization in young adult rats and no significant impact of possible stress on the S1 map plasticity (Coq and Xerri, 1999).

In a nice series of studies on the central effects of HU, Canu, Falempin and colleagues showed that the HU-induced S1 map reorganization was related to changes in reduced nerve velocity, and spinal and cortical responsiveness (Canu et al., 2003), neurotrophin expression such as NGF and BDNF (Dupont et al., 2005), cholinergic transmission (Dupont et al., 2002) and the balance between excitation and inhibition (Dupont et al., 2003; Canu et al., 2006; Treffort et al., 2006). More precisely, these authors reported that HU in adulthood increased the *in vivo* levels of both excitatory (glutamate and aspartate) and inhibitory (GABA and taurine) transmission in the L5 spinal cord (Treffort et al., 2006), while excitation levels did not change but GABA inhibition was reduced in the S1 cortex (Dupont et al., 2003; Canu et al., 2006). Thus, they showed the cortical S1 maps changes related to disuse in adulthood was mainly induced by reduced GABA inhibition but not by increased excitation. Likewise, whisker trimming, nerve transection or partial hind limb deafferentation led to a marked, but reversible reduction of GAD (gamma amino decarboxylase) immunostaining within layer IV of the cortical zone representing the deprived body part (Warren et al., 1989; Land et al., 1995; Fuchs and Salazar, 1998). Relevant to our studies is the observation that reduction in GABAergic inhibition tends also to induce cutaneous RF enlargement, as found after SMR and HU. Such a RF enlargement has been found with micro-iontophoretic injections of bicuculline methiodide to antagonize GABA-mediated inhibition in the cat S1 cortex (Dykes et al., 1984; Alloway et al., 1989).

B. Maps in the Primary Motor Cortex (M1)

The movement representations of the hind limbs in rat are located in the primary motor cortex at the rostrocaudal level of bregma, and slightly lateral (+1 to +5) to it (Strata et al., 2004; Coq et al., 2007). The representation of the hind limb joints is not topographically organized but distributed throughout the hind limb map. In control rats, the hip representation occupied in average 73.5 % of the M1 total hind limb area (3.92 ± 0.40 mm² in average), while 3.5 % was knee, 16 % the ankle, 1.5% the toes and 1.6 % was devoted to complex movements involving several joints (Coq et al., 2007; Figure 3C).

After developmental SMR, we found no change in the size of the overall M1 hind limb maps, although the proportion of hip movements increased while that of the knee decreased (Strata et al., 2004). More recently, we found slightly different results after developmental SMR. It decreased the overall size of M1 hind limb maps, although the relative areas devoted to the different joint representations were not significantly altered, except for a decrease in hip movement representations (Coq et al., 2007; Figure 3D). To our knowledge, there are no data on the effects of HU or other comparable types of disuse on M1 maps. However, neonatal amputation of the forearm induced a loss of the motor representation of this limb in the adult rat. The deafferented cortical territory was then devoted to represent movements of the trunk, shoulder and whiskers, whose cortical representation increased (Donoghue and Sanes, 1988; Donoghue et al., 1990). In contrast, whisker sensory denervation did not alter the motor representation of these whiskers, but increased the stimulation threshold (Franchi,

2000, 2001). In our study, disuse during development induced a partial deafferentation of sensory inputs, which reduces the motor representation but did not alter the muscular activation threshold. Recently, we showed that unilateral cervical spinal hemisection in adult rat drastically reduced the size of M1 forepaw movement representations and that the absence or drastic reduction of afferent inputs from S1 did not seem to be the main cause of such a large M1 forelimb map remodeling in adulthood (Martinez et al., 2010), as found after sensory facial nerve section in adult rats (Franchi, 2001; Franchi and Veronesi, 2006; see however, Liepert et al., 2003). In contrast, small and large scale changes in the M1 maps have been shown to depend mainly upon intracortical horizontal connections, synaptogenesis, and alterations of LTP/LTD and excitation-inhibition balance, all of which may lead to masking or unmasking of connections in relation to the neuronal activity within M1 cortex (Rioult-Pedotti et al., 2000; Kleim et al., 2002; see Sanes and Donoghue, 2000; Raineteau and Schwab, 2001; Teskey et al., 2008 for reviews).

In developmental disuse, although the overall M1 maps of the hind limb either decreased (Coq et al., 2007) or were not altered (Strata et al., 2004), the average thresholds (i.e. minimal amount current to evoke movements) did not differ from controls. These results differ from those of studies in which neonatal motor nerve section or limb amputation led to enlarged M1 representation of intact muscles concomitant with decreased stimulation thresholds in the newly occupied cortical territories (Donoghue and Sanes, 1987, 1988). Along the same line, sensory vibrissal pad denervation in adult rats has been found to increase the thresholds required to evoke movements of the whiskers, whereas those to produce other types of movements were similar between control and input-deprived rats (Franchi, 2001; Franchi and Veronesi, 2006). Decreased or similar thresholds seem to correspond to unmasking of pre-existing horizontal connections, whereas increased stimulation thresholds suggest high-threshold representation may be unmasked (Donoghue and Sanes, 1987; 1988; Franchi, 2001; see Sanes and Donoghue, 2000 for review).

5. Conclusion for the Disuse Model

Our studies on developmental disuse confirm and emphasize the preponderant role of individual experience in shaping the body and brain during maturation. Indeed, we have shown that abnormal inputs, through disuse, during development induced some of the motor dysfunctions (Strata et al., 2004) and hind limb histopathologies (Coq et al., 2008) which recapitulate those observed in patients with cerebral palsy (CP; Booth et al., 2001; Liptak and Accardo, 2004; Foran et al., 2005). In addition, the presence of abnormal sensorimotor experience has been shown in infants with CP (Prechtl, 1997; Hadders-Algra, 2004; Einspieler and Prechtl, 2005; Hadders-Algra et al., 2010), with its possible deleterious impact on musculoskeletal tissues (Lieber, 1986; Foran et al., 2005) and cortical reorganization in humans (Clayton et al., 2003; Hadders-Algra and Gramsbergen, 2007; Hadders-Algra, 2008; Burton et al., 2008, 2009; Wingert et al., 2008, 2009; Andiman et al., 2010). In other studies, we also showed that the combination of disuse during development with either neonatal asphyxia or prenatal ischemia increased the deleterious impact of disuse on peripheral histopathology as well as on cortical M1 and S1 reorganization (Strata et al., 2004; Coq et al., 2007, 2008; Delcour et al., 2009). It is possible that perinatal asphyxia or ischemia impinges physiological mechanisms of plasticity (see Vannucci et al., 1999; Vannucci and Vannucci,

2005 for reviews), which could even worsen the already deleterious effects of disuse during development. Thus, abnormal and limited movements, through hind limb immobilization, may account for the musculoskeletal tissue changes, which in turn contribute to provide repetitive, aberrant sensory inputs to the immature brain. These aberrant inputs induce abnormal sensory feedback leading to degradation of the topographic maps in S1 and M1 and consequently to degraded motor function.

II. Overuse Model

1. Our Animal Model of Overuse Injury

In an effort to understand the underlying mechanisms of these disorders, Barbe and Barr and a number of other labs have developed animal models of overuse injuries (Topp and Byl, 1999; Remple et al., 2001; Barbe et al., 2003; Diao et al., 2005; Sommerich et al., 2007; ; Dourte et al., 2010; Hollander et al., 2010; Willems et al., 2010). Our model is a unique rat model of voluntary repetitive reaching in which rats can be trained to perform an upper limb repetitive hand and wrist-intensive task at ranges of reach rates and force levels derived from clinical and epidemiological evidence for risk exposure in humans (See Barr and Barbe, 2002 for a review). Investigations of industrial workers by Silverstein and colleagues (Silverstein et al., 1986, 1998) defined risk levels for repetitiveness to be high when reaching and grasping motions are performed faster than 30 sec/cycle. Force is considered negligible to low if less than 15% of maximum voluntary contraction (MVC) is required and high if it is above 50% MVC. In our model, rats are trained to perform one of several levels of paced reaching and grasping tasks, as shown in Table 1. Whishaw has quantified the similarities between rats and humans in targeted reach submovements of the upper extremity (Whishaw et al., 1992). In our model, the repetition and force parameters in the rat were scaled to resemble occupational tasks in humans, as explained further in Barr and Barbe (2002). Viikari-Juntura and colleagues state that laboratory studies of animals examining the effect of repetitive loading on tissue function may be extrapolated to human exposures and responses (Viikari-Juntura, 1997; Viikari-Juntura and Silverstein, 1999). Therefore, our rat model of a paced reaching and grasping task may be generalized to humans in terms of both behavioral and tissue responses for some types of physically constrained and paced occupational tasks. An example of such a paced task would be packing, in which a worker repeatedly places small objects presented on a conveyor belt into a package crate.

In this model, rats are placed into operant test chambers for rodents with a portal located in one wall, as described previously (Barbe et al., 2003; Clark et al., 2004; Rani et al., 2009a, 2009b; Elliott et al., 2009, 2009). They are trained to perform a repetitive reaching task in which they reach through the portal to grasp and retrieve a food pellet, or to grasp and isometrically pull a force handle, which is attached to force transducer, until a predetermined force threshold is reached and held for at least 50 ms. Upon successful achievement of reach force and time criteria, the rat releases the handle and retrieves a food pellet reward by mouth from a food trough. Using this apparatus, the short-term effects (3-12 weeks) of a voluntary low force task performed at low, moderate or high reach rates, with force requirements of low

or high (see details in Table 1), on sensorimotor behavior, forelimb musculoskeletal and nerve tissues, spinal cord and brain have been determined.

Table 1. Repetitive task group parameters of the Barbe and Barr rat model of overuse

Group	Target Reach Rate (reaches/min)	Actual Reach Rate (reaches/min)	Reach Force (% of Maximum Pull Force)
HRHF	8	12	60 ± 5
MRHF	4	9.4	60 ± 5
HRLF	8	12	15 ± 5
HRNF = MRNF	4	8	<5[a]
LRNF	2	3.3	<5[a]

HRHF = high repetition high force; MRHF = moderate repetition high force; HRLF = high repetition low force; HRNF = high repetition negligible force, redefined as MRNF based on the repetition rate; LRNF = Low repetition negligible force. [a] The negligible force rats retrieved a 45 mg food pellet, which was estimated to be < 5% maximum pulling force.

Specifically, the short-term effects of repetitive and/or forceful tasks on tissue pathophysiology have been characterized, focusing on injury, inflammation, inflammation-induced catabolic changes, and fibrotic changes, that might contribute to peripheral tissue degeneration or sensorimotor behavior declines. Inflammation-induced central nervous system changes that might contribute to sensorimotor behavior changes, such as the development of pain behaviors, have also been investigated.

2. Sensorimotor Behavioral Changes with Overuse

Only a few investigative teams are studying degradation of movement and associated tissue changes in animal models of overuse injuries. The Barbe and Barr's, Sommerich's and Byl's models are the only models of repetitive motion induced overuse injuries at this time that utilize voluntary tasks in which pathophysiological tissue responses and behavioral responses, indicative of sensorimotor function, can be determined simultaneously. Voluntary movement paradigms allow the linking of tissue pathology with outward physical signs of dysfunction. The behavioral changes are discussed in this section, while possible links to peripheral and central tissue changes are discussed in a subsequent section.

a. Gross Motor Function

In the Barbe and Barr rat model, several indicators offer insight into the behavioral consequences of repetitive task performance and induced tissue changes. Reach rate (reaches/minute) is an indicator of the animals' ability to maintain task pace, and undergoes exposure-dependent declines in this model. Across weeks of task performance, rats performing a low repetition negligible force (LRNF) task showed no decrease in reach rate (Elliott et al., 2008). Rats performing a high repetition negligible force (HRNF) task had significant but transient declines in reach rate (Barbe et al., 2003; Clark et al., 2003; Coq et al., 2009), while rats performing a high repetition high force (HRHF) task demonstrate a

fluctuating and continual decline in reach rate over weeks of task performance (Barr et al., 2004; Clark et al., 2004). Grip strength is a sign of muscle integrity and mass, and declines in grip strength can result from muscle injury, neuropathic injury or muscle inflammation (described further later). In rats performing a LRNF food retrieval task, grip strength had a small but transient decline in week 6, while rats performing a HRNF food retrieval task had progressive declines in grip strength, with a 35% decline by week 6 and a 60% decline by week 8 (Barbe et al., 2008). Rats performing a MRHF handle-pulling task showed no decline in until week 12 (a 35% decline; Elliott et al., 2009a), suggesting that the handle-pulling task was easier to perform than the food retrieval task. New studies in our lab confirm that the food retrieval task required more fine motor skills to manipulate the food out of a pellet dispenser than performing an isometric pull on a fixed lever (unpublished data). In contrast, rats performing a HRHF task had progressive declines in grip strength to 53% in week 12 (Fedorczyk et al., 2010; Rani et al., 2010). Thus, gross motor function is preserved with lower demand tasks, but is more compromised with higher demand tasks, such as high repetition with high force, or tasks requiring very fine motor skills.

Task duration (number of hours/day the rats participated in this voluntary task) is an indicator of overall animal comfort. Similar to reach rate, animals exhibited exposure-dependent task avoidance with continued task performance. This was exhibited as decreased duration of performance of this voluntary task, and was likely due to discomfort from tissue inflammation, as discussed further below. LRNF rats showed no declines in task duration, HRNF/MRNF (moderate repetition negligible force task; see Table 1) rats declined transiently in week 3, MRHF rats declined only in week 12, while task duration declined progressively in HRHF rats from week 3 through 12 weeks (Barbe et al., 2003; Coq et al., 2009; Clark et al., 2004; Elliott et al., 2008; 2009a).

b. Fine Motor Skills

Movement pattern changes that are associated with chronic repetitive paw closing tasks, with or without force, have been demonstrated in both non-human primate and rodent models of repetitive motion disorder (Byl et al., 1996, 1997; Topp and Byl, 1999; Barbe et al., 2003; Sommerich et al., 2007; Elliott et al., 2008). In the Barbe and Barr model, a gradual increase in two distinct alternative reach movement patterns for food pellet retrieval was observed (Barbe et al., 2003; Coq et al., 2009). Scooping is a pattern in which the semi-open forepaw is placed over the food pellet and the pellet is dragged along the bottom or side surface of the tube and scooped into the mouth. Scooping peaked in week 5 in 47% of animals and then declined. Raking is an inefficient extreme of scooping in which repeated unsuccessful attempts to contact the food pellet with the semi-open forepaw result in repeated back and forth movements that resemble a raking motion. The raking pattern continued to increase beyond week 5 and was observed in 100% of animals by weeks 7 and 8. The “raking” reach pattern also included poor forepaw and digit closure and, thus, poor grasp control changes that are reminiscent of focal dystonia from somatosensory cortical map changes, as described by Byl et al. (1996, 1997) in an owl monkey model.

Another movement pattern degradation was increased extraneous movement reversals during the grasp phase of reach (Figure 4). All MRNF animals developed progressively increased extraneous movement reversals during the grasp phase of reach (Coq et al., 2009), while only 60% of LRNF animals developed increased extraneous movement reversals, although only transiently (Elliott et al., 2008).

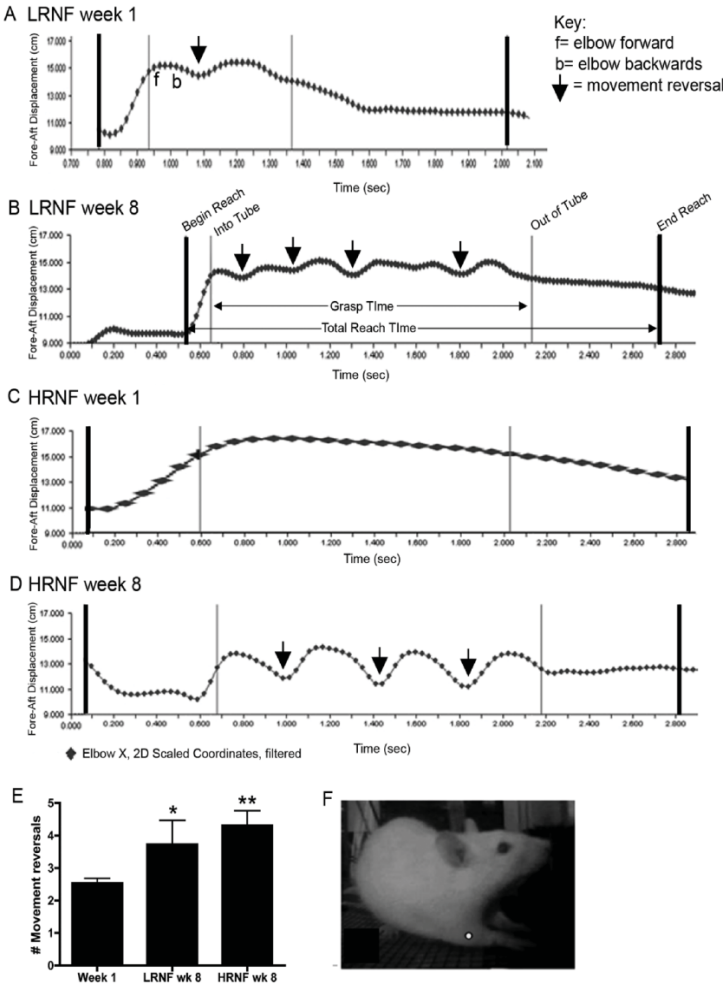

Figure. 4. Motor performance data in rats performing either a low repetition negligible force task (LRNF) or a high repetition negligible force task (HRNF) from baseline (week 1) to week 8. This task consisted of a reaching, grasping and food pellet retrieval. A-D) Representative reach sequences of LRNF and HRNF rats analyzed from video tape segments collected in weeks 1 or 8. Thick black lines indicate beginning and end time points of one entire reach, as indicated in panel B as Begin Reach and End Reach, respectively. This also defines the Total Reach Time. The thin grey lines indicate the point when the elbow enters the tube (Into Tube) and when it is withdrawn (Out of Tube). A food pellet is grasped and retrieved during this period (Grasp Time). X-axis indicates time required to perform these movements (in sec). Y-axis indicates fore-aft movement (in cm) of elbow from floor of behavior chamber, through the portal to retrieve the food, and back. Dashed lines indicate movement of elbow tracked using this 2D system. Key: f, forward movement of elbow; b, backward movement of elbow; arrows, extra movement reversals during grasp time. A-D) Not only do both LRNF and HRNF rats have more movement reversals (fore-aft displacements of elbow) in weeks 8 than weeks 1, but graph times are longer in weeks 8 than 1. (E) Mean number of extra movement reversals per reach is significantly increased in week 8 of both tasks compared to week 1, indicating more errors and thus a decline in fine motor abilities. *: $p < 0.05$, **: $p < 0.01$ compared to week 1. Mean per week ± SEM is shown. Number of animals per group: Week 1 (n = 15), LRNF 8 week (n = 7), HRNF week 8 (n = 8). F) Photo of rat showing placement of marker on elbow during analysis of video tape segments. Figure modified with permission from Elliott et al. (2008).

This latter movement pattern change was interpreted as decreased fine motor dexterity associated with declines in sensorimotor abilities, because these extra movement reversals occurring during a reach sequence are corrections for missed food pellets. These increases in arm movement reversals may be due to discomfort, changes in afferent or efferent nerve function, or both. Thus, fine motor control, like gross motor control, is preserved with lower demand tasks, but is more compromised with higher demand tasks (Elliott et al., 2008; Coq et al., 2009).

Using a voluntary repetitive pinching task in a monkey model, Sommerich and colleagues (2007) reported decreased performance as force level and pinch hold time increased. In one monkey, there was also a substantial reduction from a previously high work rate, as well as complete task cessation that lasted for days. The authors suggest that the animal was self-limiting the work rate. This suggestion may also explain the declines in task duration in our rat model.

Byl's primate model (1996, 1997) also used a voluntary task in which nonhuman primates were trained to perform stressful repetitive hand tasks of either: a) opening and closing a hand piece, or b) trying to meticulously place the thumb and the index finger on two points. Five of seven primates were trained until they could no longer perform the task. They began to have difficulty either closing or opening the hand on the target task. In addition, their training rate declined, as did their accuracy. As mentioned above, their poor grasp control changes were reminiscent of focal dystonia seen in patients. While some clinicians consider focal hand dystonia (occupational hand cramps) to be idiopathic, individuals performing tasks requiring intensive repetitive movements (e.g. working at computer, playing an instrument, pitching a ball, screwing nails, playing golf) appear to be at high risk.

C. Forepaw Sensation

Responses to sensory stimulation have also been examined in the Barbe and Barr rat model, and also appear to be exposure dependent. For example, no changes in withdrawal responses to mechanical stimulation was observed in LRNF rats across 12 weeks of task performance (unpublished observation), while MRHF rats exhibited forepaw hypersensitivity to mechanical stimuli in weeks 6 and 12 (Elliott et al., 2009a), as did HRHF rats in weeks 2-4 prior to their development of hyposensitivity to mechanical stimuli (Clark et al., 2004; Barr et al., 2004; Rani et al., 2010). The development of forepaw hypersensitivity is suggestive of an irritative nerve lesion or increased presence of nociceptive sensitization chemicals in and around peripheral nerve terminals. In contrast, the development of forepaw hyposensitivity is suggestive of a destructive nerve lesion, such as that produced by nerve compression. The presence or absence of these underlying tissue mechanisms is further discussed below.

3. Peripheral Changes with Overuse

A. Human Findings

Human studies examining tissue biopsies in patients with long-term chronic overuse syndromes find evidence of nerve compression and musculoskeletal and nerve injury, inflammation, fibrosis, degeneration and even necrosis (Ljung et al., 1999; Larsson et al., 2000; Kuiper et al., 2004; Rempel et al., 1999; Rempel and Diao, 2004; Diao et al., 2005; for more review see Barr et al., 2004). Imaging studies of patients show cortical stress fractures

(Forwood and Parker, 1991; Fredericson et al., 1995), and histological studies of articular cartilage examined after joint replacement in patients with osteoarthritis, a disorder with overuse etiology, show thinning, erosions and osteophytes. Freeland and colleagues (2002) detected increased tenosynovium IL-6, an inflammatory cytokine, and increased serum malondialdehyde, a cell injury biomarker and a reactive oxygen species that initiates arachidonic acid metabolism into products (e.g. PGE2) in patients with carpal tunnel syndrome (CTS). As mentioned earlier, increased inflammatory cytokines have also been detected in serum of patients with early onset of moderate to severe symptoms of upper limb overuse injury (Carp et al., 2007), presumably as a result of increased cytokines in injured or inflamed tissues.

B. Findings in Animal Models of Overuse

Recent work in animal models suggests that performance of repetitive tasks with or without force, induces injury, persistent inflammation, and damage in several tissues, including nerve, muscle, tendon and bone (Diao et al., 2005; Perry et al., 2005; Sommerich et al., 2007; Dourte et al., 2010; Hollander et al., 2010; Willems et al., 2010; for more review see Barr et al., 2004). In the Barbe and Barr rat model, repetitive reaching and grasping tasks induced nerve and musculoskeletal injury as well as inflammatory and degenerative responses. Specifically, observed signs of tissue injury included myofiber fray, the presence of moth eaten myofibers in forelimb muscles, declines in median nerve conduction velocity, degraded myelin and axonal swelling in the median nerve, and pathological bone morphology (Barbe et al., 2003; Clark et al., 2003, 2004; Rani et al., 2009a, 2009b; Elliott et al., 2010). The declines in median nerve conduction were exposure-dependent, ranging in reductions of 9-17% depending on the level of task intensity (Clark et al., 2003, 2004; Elliott et al., 2009b). Chronic task induced inflammatory responses were also induced, such as persistently increased macrophages and inflammatory cytokines in musculoskeletal tissues, nerves and serum (Barbe et al., 2003, Barr et al., 2003, Clark et al., 2003, Clark et al., 2004, Al-Shatti et al., 2005, Elliott et al., 2009b, Fedorczyk et al., 2010; Rani et al., 2010; Figure 5A,B). Task-induced degenerative changes also developed, including increased collagen deposition in and around the median nerve and tendon sheaths within the carpal tunnel, tendon disorganization, pathological woven bone formation as well as bone resorption (Barr et al., 2003; Fedorczyk et al., 2010; Rani et al., 2009ab, 2010). The degenerative changes, such as tendon disorganization and bone resorption, appeared to be linked at least partially to the inflammatory responses. The declines in nerve conduction velocity, nerve fibrosis, myelin degradation, axonal swelling also indicate the presence of a chronic nerve compression injury mechanism in this model, especially when high repetition is combined with high force.

4. Central Nervous System Changes with Overuse

Previous studies using animal models of repetitive motion have correlated cortical neuroplastic changes or peripheral tissue inflammation with changes in either gross or fine motor performance. However, the possibility that both peripheral inflammatory and central cortical neuroplastic changes mechanisms coexist with altered motor performance has only recently been studied (Coq et al., 2009).

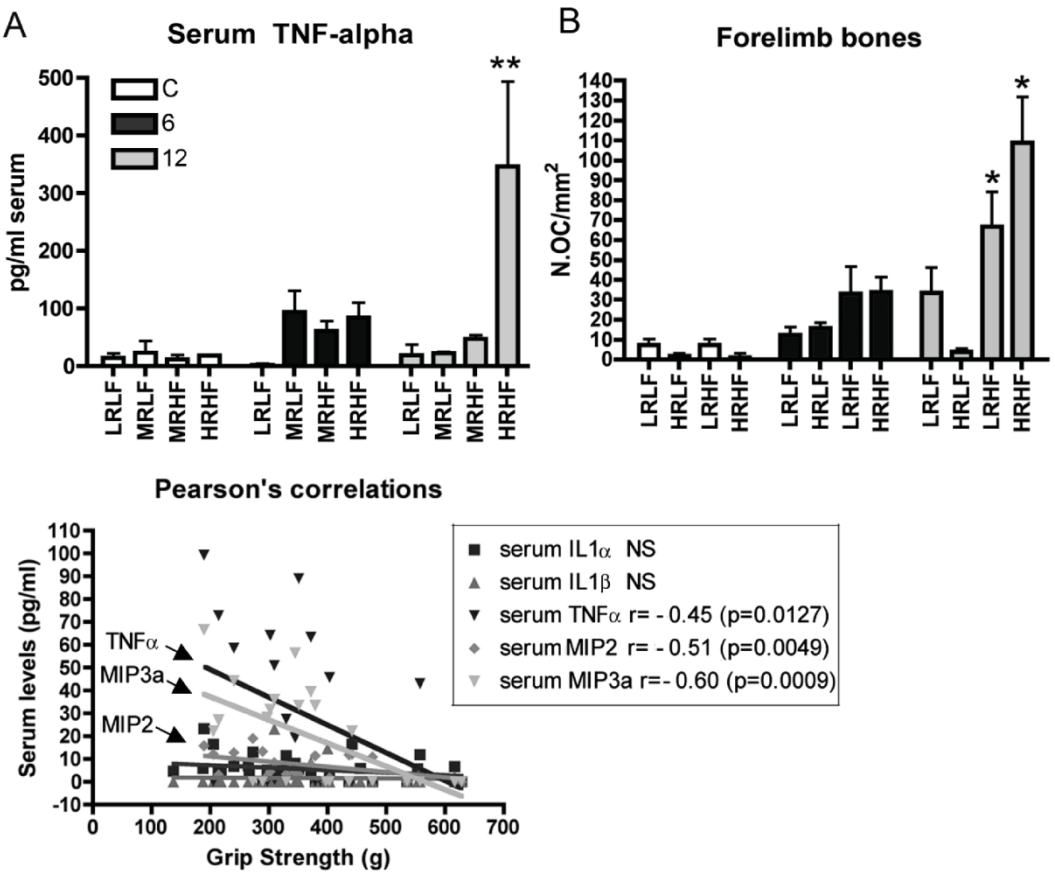

Figure 5. Task exposure dependent (i.e. dependent on weeks of task performance and demands of task) increases serum cytokines and bone osteoclasts, and correlation of grip with serum cytokines. A) Serum TNFα, a key pro-inflammatory cytokine, in all task groups at control (0), 6 or 12 weeks of task performance, tested via ELISA. Although serum TNFα was significant higher in MRLF and MRHF rats at 6 weeks compared to controls when 1 way ANOVAs were performed individually by task (see Barbe et al, 2008 and Elliott et al, 2009a), when HRHF serum data is included in a 2 way ANOVA (with factors weeks and tasks), highest serum TNFα is clearly in HRHF rats at 12 weeks. **: $p < 0.01$ compared to controls. B) Osteoclasts also increase in a dose dependent manner in distal radius and ulna with task performance, with greatest numbers ($N.Oc/mm^2$) in HRHF rats at 12 weeks. *: $p < 0.05$ compared to controls. Osteoclasts are known to increase bone resorptive activity in presence of increased TNFα. C) Graph showing Pearson's correlations of grip strength with 5 serum cytokines. Serum TNFα, MIP2 and MIP3 levels correlated negatively with grip strength. Reductions in grip strength also reduces loading on bone, contributing to decreased bone. Thus, increased serum cytokines can have detrimental effects on both motor function and bone integrity. See also Barr et al. (2004); Barbe et al. (2008); Elliott et al. (2008, 2009a) for more explanation.

We have also performed a series of studies examining peripheral inflammatory responses in combination with spinal cord neuroplastic changes (Elliott et al., 2008, 2009ab, 2010).

A. Spinal Cord Neuroplasticity

Several studies using chronic nerve compression injuries have found phenotypic changes in dorsal root ganglion neurons in which the expression of proteins, receptors, neurotransmitters, and neurotrophic factors were altered (Wallin and Schött, 2002; Hammond

et al., 2004; Chao et al., 2008). For example, Substance P increases in spinal cord dorsal horns following chronic constriction injury from partial nerve ligation, peripheral nerve injury or inflammation (Abbadie et al., 1996; Delander et al., 1997; Allen et al., 1999; McCarson, 1999; Cruce et al., 2001; Rothman et al., 2005). This increase may be due to inflammation-induced increases in afferent synaptic input to the spinal cord through an increased rate of discharge, increased peptide production by the dorsal root ganglion, and/or afferent fiber phenotype alterations that favor Substance P expression (Pitcher and Henry, 2004). Schaible and colleagues described this type of afferent influx of excitatory transmitters into the spinal cord dorsal horn after injury as the presynaptic component of central sensitization (Schaible et al., 2002). An increase in neurokinin-1, a key receptor for Substance P, occur in the post-synaptic spinal cord neurons, and most likely occurs as a response to the increased release of Substance P from nociceptive afferent terminals (Pitcher and Henry, 2004).

Thus, it was not a surprise to us to see increased Substance P and neurokinin 1 in dorsal horns in cervical spinal cord regions with performance low and moderate repetitive tasks with or without high force (Elliott et al 2008, 2009ab, 2010). In each of these studies, the neurochemical response was associated temporally with a peripheral tissue macrophage or inflammatory cytokine response. This supports a hypothesis that task induced peripheral tissue injury and inflammation drives a spinal cord neurochemical response from nociceptive afferent terminals. Such increases in Substance P and neurokinin 1 are temporally associated with mechanical hypersensitivity (Sweitzer et al., 2001; Winkelstein et al., 2001; Rothman et al., 2005). These studies combined provide evidence that spinal cord plasticity under injury and inflammatory conditions may well be contributing to chronic pain conditions, such as mechanical hypersensitivity, in animal models and patients with overuse injury.

There are also an abundance of studies showing spinal cord inflammatory responses after unilateral peripheral nerve injury, e.g. increased activated microglia and increased pro-inflammatory cytokines production by spinal cord neuron and/or glia (DeLeo et al., 1997; Hunt et al., 2001; Shubayev and Myers, 2002; Schäfers et al., 2003a; Ohtori et al., 2004; Hubbard and Winkelstein, 2005; Hatashita et al., 2008). In a recent study, we observed increased IL-1β and TNFα immunoexpression in neurons within the dorsal horn superficial lamina in aged rats that had performed a moderate demand task (HRLF) for 12 weeks, compared to normal controls (Elliott et al., 2010). We have observed that the production of cytokines in the spinal cord in our rat model includes neurons. That said, the production of cytokines by glial cells is also plausible and still needs to be investigated in our model for understanding of the central changes induced by performance of repetitive tasks.

B. Overuse-Induced Remodeling of Somatosensory and Motor Cortical Maps

With regard to the cortical changes, we examined primary somatosensory cortical (S1) and primary motor cortical (M1) changes in rats performing a reaching and grasping task with moderate repetition and negligible force demands (MRNF task) for 2 hrs/day, 3 days/wk for 8 weeks (Coq et al., 2009).

In S1, the repetitive behavioral task did not alter the overall size of the S1 forepaw map, but that overall size was positively correlated with the ratio of grip strength in week 1 versus 8. The MRNF changed the neuronal selectivity between cutaneous and nail movement inputs, as the proportion of cortical sites responding to both forepaw cutaneous stimulation and nail movements was greater in MRNF rats than in control rats. We found other examples of MRNF-induced degradation of S1 neuronal properties, such as more RFs encompassing

several forepaw subdivisions (i.e. several digits and/or palmar pads), more cortical sites exhibiting RFs located on both glabrous and hairy surfaces, and increased cortical responsiveness to light tactile stimulation. In addition, the RFs located on the glabrous forepaw were 1.5 times larger in MRNF rats than in controls and glabrous RFs overlapped much more (Figure 6A,B,D,E). The larger the glabrous RFs on the forepaw, the lower the mean percent of successful reaches. As a consequence, the forepaw representation appeared to be patchy and the S1 map topography was disrupted in MRNF rats relative to controls. For example, disruptions in the continuity of the S1 representation of contiguous skin surfaces of the forepaw and discontinuous representations of several single forepaw subdivisions into distinct cortical zones within the S1 forepaw map (see the patchy representation of digits 1 and 2 in Figure 6D), features not seen in untrained S1 maps. Another conspicuous feature in the S1 forepaw maps of trained rats was the higher proportion of RFs located on either palmer pads and digits or dorsal forepaw and wrist/forearm after the behavioral training (Figure 6E). These large RFs located on the forepaw and forearm correlated negatively with the percentage of successful reaches, positively correlated with percentage of rats using the inefficient food retrieval pattern of raking, and positively correlated with the reach phase time ratio of week 1 to week 8 (Coq et al. 2009). These data confirm and extend those found in primates in which repetitive, rewarded hand grasp led to a de-differentiation of the finger 3b maps, characterized by enlarged, overlapping RFs, the emergence of multidigit and hairy-glabrous RFs, as well as abnormal somatosensory maps in the thalamus (Byl et al., 1996, 1997; Blake et al., 2002). In previous studies, it has also been shown that abnormal sensorimotor experience (disuse) can result in a degradation of both the topographic organization of somatosensory maps and S1 neuronal properties (Coq and Xerri, 1999; Coq et al., 2008). A concordant degradation of the S1 forepaw map features has been correlated with poor tactile discrimination performance in rats (Xerri et al., 2005).

In the motor cortex, the MRNF reaching task drastically increased the total area of the forepaw movement representation (1.6 times larger) compared to controls. The areas occupied by the shoulder (6% of the total map area), elbow (41%), wrist (23%), digits (1%) and arm (3%) were not significantly affected by the behavioral training, but the cortical area devoted to multi-joint movements drastically increased in MRNF rats (Figure 6C,F). Indeed, the movement representation area of the elbow-wrist multi-joint responses tripled and the arm-digits multi-joint areal extent was 17 times larger than in untrained rats. Interestingly, the cortical increase in the multi-joint movement representation for elbow-wrist, arm and arm-digits correlated strongly with the increased prevalence of the raking strategy, as well as the elbow movement representation. The overall threshold (i.e. minimal current to evoke a movement) of neuronal M1 responses did not differ between groups nor did the threshold for most forelimb joints, except for digits (digits only and digit-arm), which were 2 times lower after behavioral training. Out of the motor forepaw map, the average thresholds required to evoke whisker and hind paw movements did not differ between both groups, so that the MRNF task specifically altered the M1 digit representation.

Thus, the MRNF task drastically increased the size of the M1 forepaw maps, especially the movement representation of the digits, digit-arm and elbow-wrist specifically involved in the behavioral task, and also decreased specifically the amount of current required to evoke movements of the digits. To a certain extent, the motor cortical reorganization induced by the prolonged performance of repetitive reaching in our model seems more adaptive than deleterious.

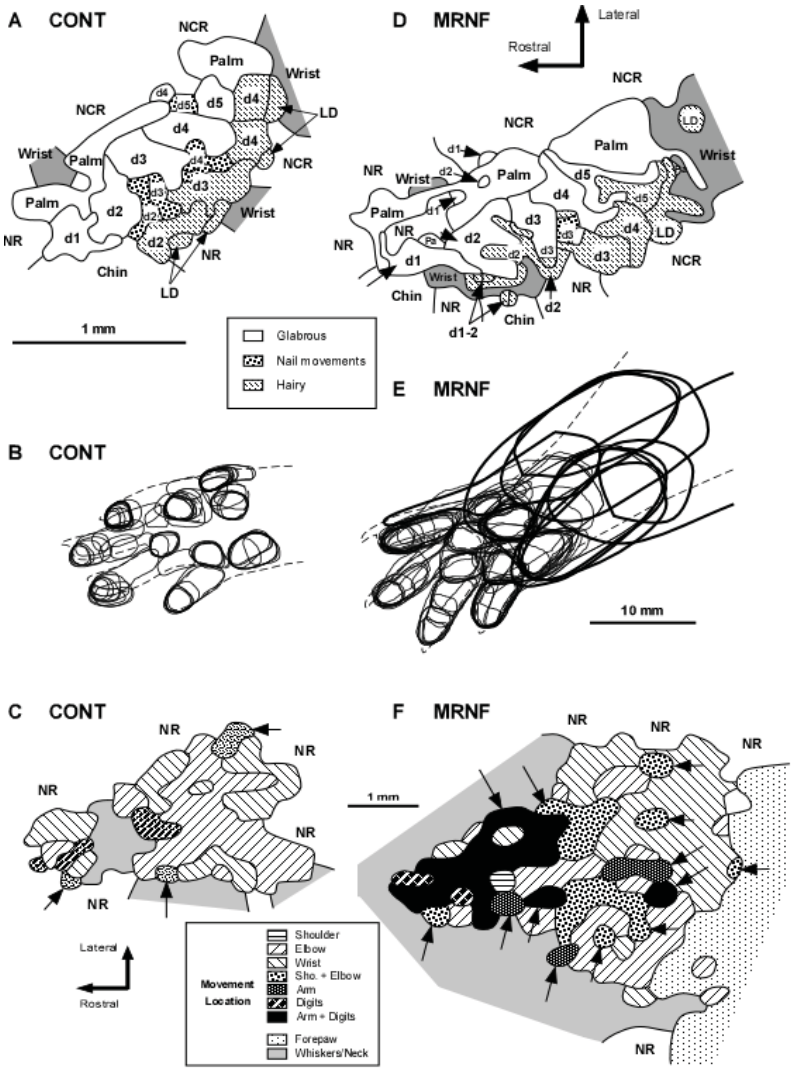

Figure 6. Primary somatosensory (S1) and motor (M1) cortical maps of the forepaw in control (CONT) and trained rats performing a moderate repetition, negligible force (MRNF) task. A) Representative S1 map devoted to the forepaw skin in a normal control rat. B) Typical glabrous receptive fields (RFs) in the same normal control rat showing single RFs encompassing mainly one or two forepaw subdivisions. C) Cortical map of the movement representation of the forepaw joints in a normal control rat. D) Representative map in an 8 week MRNF rat showing disruptions in the continuity of the S1 representation of contiguous forepaw skin surfaces and patchy representations of single forepaw subdivisions (e.g. digits 1 or 2; examples indicated by arrows) into distinct cortical zones. E) Glabrous RFs in the same MRNF rat showing many large RFs encompassing several forepaw subdivisions and even larger RFs located on both plantar pads or digits and wrist/forearm (examples indicated by thick RFs). Note the greater overlap of glabrous RFs in MRNF rats (E) than in CONT (B). F) Typical map in an 8 week MRNF rat showing a drastic enlargement of the M1 forelimb cortical map and the task-induced increase in the cortical area devoted to digit, arm-digit and multi-joint movements (multi-joint responses are highlighted by arrows). Abbreviations: d1-d5, digit 1 to digit 5; LD, large dorsum of forepaw; NCR, non cutaneous responses; NR, no response; Pa, palmar pads; Sho., shoulder. Figure modified with permission from Coq et al. (2009).

Several studies examined the effects of motor repetition related to any motor training experience on the M1 map organization. Extensive repetition of digit movements without motor learning in primate or unskilled pellet reaching in rats did not significantly alter the M1 forelimb map, while motor skill learning was associated with an expansion of the representation of distal forelimb movements (Kleim et al., 1998; Plautz et al., 2000). The M1 skill-related expansion has been shown to depend upon functional synaptogenesis (Kleim et al., 2002, 2004), long-term potentiation (Rioult-Pedotti et al., 2000), excitation-inhibition balance (see Teskey et al., 2008 for a review), synchronous firing (Schieber, 2002), tuning and signal-to-noise changes of M1 cells (Kargo and Nitz, 2003, 2004). In rats that reached for bundles of pasta strands, skilled reaching with targeting and grasping components requires coordinated forelimb joint movements (Remple et al., 2001). We also observed increases in elbow-wrist and in digit representations in our overuse model that are consistent with such increased skill. These findings support the learning hypothesis for the etiology of repetitive motion disorders (Byl and Melnick, 1997; Blake et al., 2005, 2006).

5. Links between Behavioral Changes and Peripheral and/Or Central Changes

A. Peripheral Sensitization

In our model, several peripheral tissue changes are associated temporally and correlate statistically with declines in reach performance, grip strength, agility and mechanical hypersensation. These changes include widespread musculoskeletal and peripheral nerve inflammation, nerve pathology, and perhaps musculoskeletal tissue injury. With regards to inflammation, we have observed that reach rate correlates negatively with changes in nerve and musculoskeletal inflammatory cytokines and macrophages (Barbe et al., 2003; Clark et al., 2003, 2004; Elliott et al., 2008, 2009a), as did grip strength (Barbe et al., 2008; Elliott et al., 2009ab; Fedorczyk et al., 2010; Rani et al., 2010). This latter finding is supportive of other work in which forelimb grip strength declines occurred after intramuscular injections of TNFα (Schäfers et al., 2003b; Beyreuther et al., 2007), suggesting that reduced grip strength can be a sign of muscle inflammation (also called muscle hyperalgesia). In a recent study from our lab, a two-week regimen of an anti-TNFα drug decreased repetitive task-induced increases of TNFα in flexor forelimb muscles and attenuated declines in grip strength (Rani et al., 2010). Grip strength was not entirely restored due to the presence of increased Substance P and neurokinin 1 in the spinal cord of these same rats (unpublished data), suggesting a central sensitization mechanism was also present that 2 week regimen of anti-TNFα could not ameliorate. Our observed degraded forelimb movement patterns, such as scooping and raking, was also concomitant with forelimb musculoskeletal and nerve inflammation (Barbe et al., 2003; Elliott et al., 2008; Coq et al., 2009).

Lastly, heightened pain sensitivity is a known consequence of increased inflammatory mediators, particularly TNFα. Pro-inflammatory cytokines activate and sensitize peripheral terminals of nociceptors both directly (such as within the nerve) and indirectly (such as in surrounding tissues) leading to hypersensitivity (Moalem and Tracey, 2006; Schäfers and Sorkin, 2008). We have recently reported a correlation between increased inflammatory

cytokines in the median nerve and forepaw mechanical hypersensitivity (Elliott et al., 2010). Alternatively, a task-induced systemic cytokine response may also be associated with the widespread mechanical hypersensitivity found in the present study; we have previously observed a significant correlation between reduced grip strength and task-induced increases in serum inflammatory cytokines (Barbe et al., 2008; Elliott et al., 2009; Figure 5C). These findings combined suggest that inflammation-driven peripheral sensitization contributes to sensorimotor changes with performance of repetitive tasks.

B. Peripheral Nerve Injury

A peripheral nerve injury mechanism has also been identified in our overuse model. We have observed nerve demyelination, axonal swelling, fibrosis, with subsequent decreased nerve conduction velocity, forepaw sensation and grip strength, each suggestive of a nerve compression injury (Clark et al., 2003; 2004; Elliott et al., 2010). Declines in grip strength can also be a sign of neuropathic injury (Schäfers et al., 2003a; Beyreuther et al., 2007). The contribution of nerve injury to grip strength changes in our model is supported by positive correlations grip strength declines and reductions of median nerve conduction velocity (Elliott et al., 2009, 2010). In conclusion, our findings suggest that several sensorimotor behavior outcomes are affected by peripheral muscle and nerve inflammation, nerve compression injury, or both, with performance of repetitive tasks.

B. Spinal Cord Central Sensitization

The phenomenon of central sensitization is characterized by adaptations in neurons and glia cells, such as changes in neuronal structure, protein production, function, and survival within the CNS, that then contribute to abnormal pain behaviors (Woolf and Salter, 2000). For example, it has been proposed that spinal cytokines released in the dorsal horn nerve terminal region ipsilateral to the affected peripheral nerve spread to nearby spinal nerve terminals that then effect uninvolved peripheral nerves and central sensory processing (Chacur et al., 2001). These changes may then promote remote and contralateral sensitization effects (Chacur et al., 2001). We have observed forepaw hypersensitivity bilaterally in our model (Barr et al., 2004, Elliott et al., 2010). However, we have also shown that the non-reach limb is used as a support limb in our model, as depicted in Fedorczyk et al. (2010). Thus, the bilateral hypersensitivity responses in our study are not a type of 'mirror allodynia', sometimes seen after unilateral nerve ligation, in which there is a contralateral spread of symptoms via spinal cord mechanisms (DeLeo et al., 1997; Chacur et al., 2001; Milligan et al., 2003; Kelly et al., 2007), but rather due to bilateral use of the forelimbs in performing the task, and then bilateral changes in the median nerves.

However, we have also reported the presence of hind paw mechanical hypersensitivity in our model (Barr et al., 2004; Elliott et al., 2010), limbs not involved in performing an upper extremity repetitive task. We observed hind paw mechanical hypersensitivity in aged rats performing a HRLF task for 12 weeks (Elliott et al., 2010), and an early increase in hind paw sensitivity at 3 weeks in young rats performing a HRHF task (prior to the development of hyposensation in these latter rats). These findings are suggestive of an extraterritorial spread of symptoms via central sensitization mechanisms that may contribute to pain behaviors with overuse injuries. Studies showing mirror allodynia (mechanical hypersensitivity) or extra-territorial hyperalgesia in cases of unilateral nerve injury provide evidence of nerve injury-induced mechanisms of central sensitization (Chacur et al., 2001; Gazda et al., 2001). We

suggest that the hypersensitivity in the uninvolved hind paws in our model may be due to increased pro-inflammatory cytokines in cervical spinal cord affecting cells or processing in distal spinal cord segments. Unfortunately, we did not collect lumbar spinal cord segments in these studies, and therefore are limited in our interpretation of these results. Nevertheless, the finding of mechanical hypersensitivity in body regions not involved in performing a task is highly suggestive of central mechanisms of sensitivity and is of potential interest to clinicians considering appropriate therapies for patients with overuse injuries.

C. Does Sensitization Result from both Peripheral and Central Changes?

Signs of injury and inflammation occurring in the median nerve in addition to the spinal cord inflammatory response prevent us from separating peripheral versus central mechanisms contributing to observed cutaneous sensation changes in forepaws. Pro-inflammatory cytokines have been shown to sensitize peripheral terminals of nociceptors both directly and indirectly, leading to hypersensitivity (Moalem and Tracey, 2006; Schäfers and Sorkin, 2008). We have reported the presence of inflammatory cytokines in peripheral nerves, musculoskeletal tissues, and circulating widely in serum in our model (Al-Shatti et al., 2005; Barbe et al., 2008; Coq et al., 2009; Elliott et al., 2009, 2010). We have also reported statistical correlation between these cytokine increases, hypersensitivity and declines in grip strength in several studies, suggesting a link between increased peripheral cytokines and pain-related behaviors with overuse injuries.

Furthermore, nerve compression can be initially irritative to nerves, resulting in cutaneous hypersensitivity. Our findings of mechanical hypersensitivity in the presence of decreased nerve conduction velocity, and histological findings of increased extraneuronal connective tissue and axonal swelling in the median nerve, are suggestive of nerve compression with long-term repetitive task performance, particularly HRHF tasks. Hand and arm pain in the distribution of the median nerve is a common symptom in patients with electrophysiologically diagnosed carpal tunnel syndrome, particularly in those subjects involved in full time intensive manual work (Bonfiglioli et al., 2007).

With regard to central sensitivity, we can only point to an abundance of other studies showing spinal cord inflammatory responses after unilateral peripheral nerve injury, e.g. increased spinal cord neuron- and glia-produced cytokines, increases that are temporally associated with mechanical hypersensitivity (DeLeo et al., 1997, Hunt et al., 2001, Shubayev and Myers, 2002, Schäfers et al., 2003b, Ohtori et al., 2004, Hubbard and Winkelstein, 2005, Hatashita et al., 2008). The contribution of central sensitization to repetition-induced hypersensitivity is also suggested by studies from our lab showing increased Substance P and neurokinin-1 receptor in spinal cord dorsal horns, changes described earlier (Elliott et al., 2008, 2009ab). These increases in Substance P correlated statistically with declines in forelimb grip strength (Elliott et al., 2009b), and coincided with degraded forelimb movement patterns (Elliott et al., 2008). On the other hand, we have also observed increased Substance P in forelimb tendons with HRHF task performance, changes that correlated strongly with declines in grip strength (Fedorczyk et al., 2010), bringing us back to a potential peripheral sensitization mechanism. We hypothesize that both mechanisms are at work in our model and cases of overuse injury in which chronic pain is present.

D. Contribution of Cortical Map Changes to Sensorimotor Behavior Changes

It is now well established that S1 map organization and neuronal properties are correlated with sensorimotor and tactile performances (Xerri et al., 2005; Duncan and Boynton, 2007; Bensmaia, 2008; Reed et al., 2008). The deterioration of the S1 map features and neuronal properties found in our model, described earlier, would likely result in ambiguous interpretation of tactile cues and undoubtedly contributed to a decline in grasp control, ultimately resulting in failed and repeated grasp attempts (i.e. the increased movement reversals observed in our model). Our observed "raking" reach pattern also includes poor forepaw and digit closure and, thus, poor grasp control changes that are reminiscent of focal dystonia as described by Byl et al. (1996, 1997) in an owl monkey model. In fact, in our Coq et al. (2009) study, the enlargement of S1 receptive fields and the emergence of large receptive fields that encompassed the whole forepaw (digits and palmar pads) or dorsal hand and wrist or forearm correlated statistically with a reduction in successful reaches, an increase in the inefficient raking food retrieval pattern, and an increase in reach time. These findings support our hypothesis that ambiguous interpretation of tactile cues result in reduced motor performance, particularly fine motor skills, as found in the monkey model of focal hand dystonia (Byl et al., 1996, 1997; Blake et al., 2002).

Similar movement pattern changes have been attributed to degradation of the S1 paw representation in owl monkey (Byl et al., 1996, 1997; Topp and Byl, 1999). Using somatosensory evoked potential measurements, Byl et al. (2000, 2002) detected somatosensory disorganization consistent with somatotopic dedifferentiation in human subjects with severe and moderate focal hand dystonia. These observations have led to a learning hypothesis for the origin of focal hand dystonia, and possibly other repetitive motion disorders, whereby the reversibility of the somatosensory cortical degradation is exploited in treatment interventions to restore normal cortical representations (Byl and Melnick, 1997; Byl and McKenzie, 2000; Byl, 2003, 2007; Byl et al., 2003; Candia et al., 2003; McKenzie et al., 2003).

The motor declines also correlated with a dramatic enlargement of the overall forepaw map area of the primary motor cortex, in which emerged the representation of joint movements specifically involved in the repetitive task. In fact, the movement representation areas leading to multi-joint movements, such as elbow-wrist, arm and mainly wrist-digits, increased in repetitive task rats. Interestingly, this increase in cortical multi-joint movement representations correlated strongly with the increased prevalence of the raking strategy.

Unexpectedly, but interesting to consider here, task-induced peripheral increases in inflammatory cytokines in muscles of repetitive task rats had a strong negative correlation with not only grip strength, but also with the amount of current required to evoke movements of the wrist, and elbow-wrist, and arm-digit multi-joints in the primary motor cortex. The higher the inflammation in flexor muscles specifically involved in the task, the lower the threshold required to elicit arm-digit movements, which was decreased in trained rats relative to controls.

6. Conclusions for Overuse Injury Model

Our data from a rat model of overuse injury show that peripheral nerve injury, peripheral inflammatory, spinal cord sensitization and central neuroplastic mechanisms co-exist. Each

appear to contribute to motor behavior declines and the development of pain related behaviors. What was previously unknown was if peripheral inflammation was primarily responsible for the movement performance deficits that emerge in these rats over time (Barbe and Barr, 2006) or whether cortical degradation was responsible for the movement defects (Byl et al 1997). It is clear from our studies that *both* sensorimotor cortical reorganization and peripheral inflammation/injury mechanisms contribute to movement performance declines and movement pattern changes in the progression of the overuse injury.

Overall Conclusion

In conclusion, both prolonged disuse and overuse lead to both peripheral and central changes that are interdependent to drive cerebral plasticity and altered output function. From the findings of these two models combined, we postulate that abnormal movements, whether limited through hind limb immobilization, or excessive as in highly repetitive tasks, can lead to pathological musculoskeletal tissue changes, which in turn contribute to provide aberrant sensory inputs to the brain. These repetitive, aberrant inputs result in abnormal sensory feedback leading to S1 and M1 topographic reorganization, which can be either adaptive or deleterious. Indeed, sensorimotor disuse, rewarded-training and overuse drive long-term potentiation and depression (LTP and LTD), spike-timing dependent plasticity (STDP), homeostatic synaptic and structural plasticity in both S1 and M1 cortices (see Adkins et al., 2006; Moucha and Kilgard, 2006; Martin et al., 2007; Feldman, 2009; Wittenberg, 2010). Thus, disruptions in the S1 map topography and neuronal properties, as described in our models, suggest less ability to interpret inputs to selected parts of the body and the abnormal feedforward of somatosensory information to the motor cortex might be subsequently expressed in degraded motor functions, as found in patients with CP or focal hand dystonia (Byl, 2004; Gordon et al., 2006; Wingert et al., 2008, 2009, 2010; Burton et al., 2009; Hinkley et al., 2009).

Therefore, our studies emphasize the crucial role of early sensorimotor experience and suggest the critical importance for early interventions and sustained activity in children and infants with CP to hopefully restore sensorimotor functions or at least prevent further degradations (Damiano, 2006, 2009; Hadders-Algra and Gramsbergen, 2007). Our studies also emphasize the need for early intervention in repetitive/overuse injuries to reduce central phenotypic changes in dorsal root ganglia, spinal cord and cortical cells, in which the expression of proteins, receptors, neurotransmitters, and neurotrophic factors have been altered as a consequence of either chronic nerve compression injuries, chronic inflammation (local, widespread or systemic) and subsequent aberrant sensory inputs (Latremoliere and Woolf, 2009; Sorkin and Yaksh, 2009).

Acknowledgements:

The work described in this review paper from the laboratory of Dr. J-Olivier Coq was supported by CNRS, Ministère de l'Enseignement Supérieur et de la Recherche, l'Agence Nationale de la Recherche, la Région Provence-Alpes-Côte-d'Azur, NIH grant NS-10414, the

Cerebral Palsy Institute, la Fondation Motrice, Fondation NRJ – Institut de France and the Sandler Fundation. The work described in this review paper from the laboratory of Dr. Mary Barbe was supported by a grant from NIOSH grants UO1 OH 03970 and RO1 OH 8599, and NIAMS grants R01 AR056019 and R01 AR051212.

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