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The importance of the quadruped animal model in functional neurorehabilitation for human biped

REVIEW

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Abstract

Functional neurorehabilitation (FNR) is an alternative approach to improve patient's quality of life. FNR has neuroanatomical foundations and is based on two properties of the central nervous system (CNS), which are present both in human biped and quadruped animal: neuroplasticity and neuromodulation. The dog and cat models, by their very own characteristics, become an evidence model for the human biped. In the human biped we can apply locomotor training according to the norms of locomotor training for fictive locomotion in quadruped.

Keywords
Functional neurorehabilitation; central nervous system; neuroplasticity; neuromodulation; locomotor training; fictive locomotion; pyramidal; extrapyramidal; motor spinal input; central pattern generators.

Introduction

The spinal cord in human biped is the most caudal division of the central nervous system (CNS). It is a fundamental structure in mediating the execution of voluntary and reflex arc movements. It contains neural circuits that control some types of movement, some of which located exclusively in the spinal cord. Therefore, the brain only sends command "signals" for modulating, activating, or suspending the movement. The motor gait pattern itself is located in the spinal cord (Barros & Pinheiro, 2014).

In the canine quadruped, the extrapyramidal system is responsible for maintaining posture, rhythmic and semi-automatic activities, such as locomotion (Thomson & Hatin, 2012). The extrapyramidal system tract for upper motor neuron (UMN) originates in the brainstem and is of the utmost importance (Thomson & Hatin, 2012).

In the human biped, the UMN system originated by the motor cortex is responsible for the voluntary movements of the face, carpus and limbs, using the pyramidal, corticonuclear and corticospinal tracts (Thomson & Hatin, 2012).

In summary, human bipedal is pyramidal and quadruped animal is extrapyramidal (Barros & Pinheiro, 2014; Solopova *et al.*, 2015; Thomson & Hatin, 2012). This statement allows interrelating functional

rehabilitation in human medicine (HM) with veterinary medicine (VM), leading to the application to HM of exercises specific to VM.

Since the spinal cord has activity in itself, we can perform an interchange of functional neurorehabilitation (FNR), considering that dogs are extrapyramidal, with the rubrospinal tract (RuST) acting as corticospinal tract (CST), whereas in HM the CST is the main downward tract for motor action, as mentioned above (Lorenz *et al.*, 2011).

FNR is an area of physical medicine which aims at utilizing the motor cortex, brainstem and spinal cord neuroplasticity property, as to promote independence functions and quality of life, both for the quadruped animal and biped human (Thompson & Walpaw, 2014).

Neural plasticity in human biped and quadruped animal

A comprehensive review study allows us to ascertain that when the biped human has the corticospinal paths damaged, it may, through its neuroplasticity property, promote extrapyramidal paths to be the paths of connection and information from the motor cortex to the spinal cord (Garcia *et al.*, 2015). Indeed, anatomical and functional studies have demonstrated that the motor cortex is connected to the spinal cord, not only by the CST, but also, indirectly, by the motor pathways of the brainstem (Garcia *et al.*, 2015).

Through various studies we are able to prove the neuroplasticity property of the nervous system, which is responsible for the success of FNR and of spontaneous or fictive locomotion (Garcia *et al.*, 2015). Hence the adaptation of rehabilitation exercises in quadrupeds to bipeds is explained on a neuroanatomical basis, and it may promote faster locomotion, as well as a more accurate performance (Garcia *et al.*, 2015).

The potential neuroplasticity ability of the reticulospinal tract (RST), a brainstem motor tract, promotes motor functionality and fine movements function in the thoracic limbs (Garcia *et al.*, 2015).

Within FNR, we demonstrate how exercises that stimulate the spinal locomotor circuits play a key role in attaining the locomotion ability both on quadrupeds and bipeds.

Neurorehabilitation is fostered by the neuroplasticity of the motor cortex, brainstem and spinal cord (Thompson & Walpaw, 2014).

Over the years, it has been proved that, in mammals, the spinal cord has an intrinsic capacity to generate rhythmic motor patterns, without sensory or motor supraspinal input (Chang, 2014; Gad *et al.*, 2012). Grillner calls this ability of the spinal cord of spinal neural circuits of central pattern generators.

Supraspinal control is however essential for a coordinated and even conscious locomotion. In quadrupeds, locomotion is characterized by the coordination of forelimbs and hind limbs, which is generated by the same spinal neural control mechanism (Cazalets & Butrand, 2000; Nathan, Smith & Deacor, 1996). This coordination between the two motor systems (upper motor neuron - UMN; lower motor neuron - LMN) is present in the quadruped locomotion and preserved in biped locomotion.

The neuroplasticity property allows the biped to use, for locomotion, the cerebellum and the brainstem when it exhibits complete or incomplete spinal cord injury, after receiving the stimulus of a locomotor training. Therefore, it is assumed that the two-legged and four-legged supraneural plasticity is associated with the plasticity of the neural spinal circuits (Tansey, 2010).

The above facts seem to indicate that FNR should explore the plasticity of neural circuits both at a supraspinal and spinal level.

Several studies have demonstrated how repeated rehabilitation exercises that stimulate the afferent and efferent sensory-motor pathways allow the spinal neural circuits to memorize the rehabilitation exercises which were practiced, and thus the neurorehabilitation will depend on repetition and qua-

lity of the locomotor training (Nielsen *et al.*, 2015; Zhong *et al.*, 2012).

Proving that FNR has clinical success are several experiments in cats and rats where, after a complete transaction, the spinal cord alone allows the capacity of a locomotion pattern. The FNR training consisted of daily locomotor training in a treadmill for at least 30 minutes, 5 to 6 times a week. Following 2 to 3 weeks of training, the animals showed fictive locomotion (Nielson *et al.*, 2015; Zhong *et al.,* 2012).

Within FNR, neuroplasticity must be used by the rehabilitator as to allow a connection between plasticity and functionality and, thus, rehabilitation exercises that induce plasticity should avoid erroneous adaptations which cause pain and spasticity (Nielson *et al.*, 2015).

On that account, neurorehabilitation must have pain management has one of its purposes, hence stimulating the spinothalamic tract (Nielson *et al.*, 2015; Thomson & Hatin, 2012).

Activation of central pattern generators (CPG) in human biped and quadruped animal

The CPG activation can be via epidural, as explained by Edgerton in several studies. In recent studies, two types of stimulation are indicated, the epidural stimulation (ES) and the intraspinal stimulation (IS), proving that simultaneous ES and IS stimulation provide a more consistent performance of the pelvic limbs, compared to ES and IS isolated. ES and IS being potentiated together means that they have different neural mechanisms: ES promotes stimulation of the dorsal lumbosacral spinal cord intumescence, and therefore of the reflex arc, allowing a motion gait with the hind limbs on the treadmill, although not rhythmically synchronized with the forelimb; whilst IS promotes the stimulation of the propriospinal pathways, associated or not with the locomotor areas of the brainstem. Hence, the simultaneous activation of ES and IS allows the engagement of interneural population which regulates locomotion (Lavron *et al.*, 2015; Shah *et al.,* 2013).

We can say that the central pattern generators are involved in locomotion of both biped and quadruped, and in both they work depending on the supraspinatus input and sensory feedback. The lumbosacral spinal cord intumescence has the CPG that promote a rhythmic activity, without supraspinal action, and thus in human biped it is suggested by evidence that movements produced in locomotion, race, swim, etc. use the rhythmic circuits of CPG (Solopova *et al.*, 2015).

Currently, it is proven that electromyostimulation of peripheral nerves, as well as cyclical movements, increase the excitability of the segments of the spinal cord, thereby facilitating the emergence of a movement similar to locomotion. In the case of cyclical movements, cycles of 2 up to 10 are necessary to promote a gear movement similar to voluntary gait.

We can summarize by saying that the stimulation may be, as stated above, by electric epidural stimulation, but also by transcutaneous stimulation, direct electromagnetic stimulation of the spinal cord and rhythmic movements in standing posture, depending on the supraspinal influence and on the rhythmic capacity of the spinal circuits (Musienko *et al.,* 2012; Solopova *et al.,* 2015).

Voluntary locomotion allows a voluntary activation of the CPG, making it easier to stimulate the transcortical reflex pathways and increasing the depolarization of motoneurons. Therefore, all FNR modalities that activate CPG must be associated to a locomotor training as to attain involuntary and voluntary locomotion more similar to normal (Harkema *et al.*, 2012; Musienko *et al.*, 2012; Solopova *et al.*, 2015).

For years it has been proven that the ES is a modality of FNR with clinical application in quadruped and biped with spinal cord injuries (Nandra & Edgerton, 2011), furthermore, numerous experiments prove that the effect of ES can be complement and enhanced when combined with the prescription of

drugs, such as serotonergic 5HT agonists, and locomotor training (Angeli *et al.*, 2014; Gad *et al.*, 2012; Gerasimenko, 2010; Lavron *et al.*, 2014).

K. Thompson and R. Walpaw indicate that the human biped, after an incomplete spinal cord injury, has a motor disability, namely spasticity and poor motor control, making all FNR modalities that activate CPG and stimulate neural plasticity relevant for rehabilitation; furthermore, the authors indicate that movements with higher amplitudes promote the diminishment of muscular spasticity and improve balance (Thompson & Walpaw, 2015).

Finally, after a 35 year lasting study, a new capacity of the nervous system is addressed, recognizing that most spinal cord injuries are incomplete and fit for regeneration, making FNR therapies fundamental for motor success (Thompson & Walpaw, 2014).

All FNR protocols are based on neural plasticity and suggest a complementary therapeutic method for recovering functionality (Thompson & Walpaw, 2014; Thompson & Walpaw, 2015). These exercises induce plasticity to the neuro-spinal reflexes, after severe injury to the spinal cord, leading to the fictive locomotion gait, or "spinal walking" (Harkema *et al.*, 2012; Thompson & Walpaw, 2014).

"Spinal walking"

Since 1966, experiences show that the mesencephalon nuclei are specific areas, identified as mesencephalon locomotor region (MLR). Descending spinal pathways are originated in the MLR and are projected into the medial reticular formation and ventral portion of the spinal cord. Ascending pathways can activate the MLR regions via the locomotor pons-medullar route region (LPR). The MLR can also be stimulated by dorsolateral funiculus (DLF) fibers, originated between C1 and L1 spinal cord segments. These fibres (DLF and LPR) can induce a quadruped locomotor gait through the brainstem (Lavron *et al.*, 2014; Harkema *et al.*, 2012; Musienko *et al.*, 2012).

The same experiments also demonstrate that CPG can be activated by intraspinal and epidural routes, as mentioned above. A spontaneous locomotion might be achieved, since there is a specialized region of the upper portion of the lumbosacral region that includes an ample neural circuit for generating a spontaneous locomotion in the quadruped (Chang, 2014; Lavron *et al.*, 2014).

The above mentioned is demonstrated by experiments in cats and rats that demonstrate how neuromodulation of electric stimulation and drugs are more effective in promoting an autonomic sensory-motor function after a spinal cord injury (Gad, 2012; Lavron *et al.*, 2014; Musienko *et al.*, 2012). The same is proven in regards to neuromodulation and voluntary control in a paralyzed biped (Angeli *et al.*, 2014; Lavron *et al.*, 2014).

Neuromodulation of the Motor Neuron

Depolarizing currents mediated by sodium and calcium channels that have the ability to convert motor neurons from mere passive pathways to active precursors of electric signals are designated as *Persistent Inward Currents* (PICs). PICs depend on the presence of monoamines, such as serotonin and norepinephrine, produced by groups of cells located in the brainstem that project their axons to the spinal cord segments. Thus, serotonin and norepinephrine work as neuromodulators affecting the PICs and the motor neurons (Heckman, 2014).

In decerebrised cats, the spinal cord transection damages the brainstem monoaminergic pathways, as well as all descending caudal pathways to the spinal cord transection, eliminating the effects of PICs and PICs themselves. Likewise, in animals with incomplete spinal cord injuries PICs are still produced, however, their amplifying effect is not achieved and therefore muscle activation does not occur (Heckman, 2014; Levine *et al.*, 2011; Musienko *et al.*, 2012).

PICs amplify the excitation or inhibition of the electrical current in spinal motor neurons, but these are lost in the event of acute spinal cord injury.

However, they can be recovered after a period of 1 to 5 months after spinal cord injury, despite losing normal specificity.

Musculoskeletal system

The musculoskeletal system, in mammals, allows postural control and movement patterns with diverse intensity (Baldwin *et al.*, 2013).

The motor unit, in the human biped and quadruped animals, comprises all the muscle fibres innervated by a single motor neuron (Ropper, Samuels & Klein, 2014).

In the human biped, locomotion requires the standard postural extensor reflex to be inhibited and the coordination pattern of the walking movement to be implemented, with the complicity of the multisegmental spinal reflexes and of the brainstem locomotor centres (Ropper, Samuels & Klein, 2014).

The control of the musculature of the proximal limb muscles is mediated by the RST and vestibulospinal tract (VST), while the control of the distal musculature is mediated by the RuST and CTS tracts (Ropper, Samuels & Klein, 2014).

The muscle tone depends on the alpha and gamma motor neurons. The gamma motor is actively tonic at rest, making the intrafusal fibres taut and sensitive to active or passive muscle length changes (Ropper, Samuels & Klein, 2014). This phenomenon, in quadruped animals, is called alpha and gamma co-activation (Thomson & Hatin, 2012).

The excitability of the alpha and gamma motor neurons defines the level of activity of the reflexes and muscle tone, yet it is affected by the descending fibre system (Ropper, Samuels & Klein, 2014).

The Golgi tendon organ receptors can monitor the strength of contraction and the length of the muscle fibres (Ropper, Samuels & Klein, 2014).

The flexion of the limb will cause stretching of the extensor muscles and the extension of the muscles will cause stretching of the flexor muscles. The two will induce the myotatic reflex, which leads to the contraction of the stretched muscles (Thomson & Hatin, 2012).

Somatic Motor System

The UMN system is classified anatomically in pyramidal and extrapyramidal system (Thomson & Hatin, 2012).

The CST represents between 20 to 30% of the white matter of the spinal cord in primates, while in carnivores it represents only 10% (Ropper, Samuels & Klein, 2014; Thomson & Hatin, 2012).

The red nucleus of the brainstem receives, ipsilaterally, nerve fibres from the motor cortex, projecting it to the spinal cord under the form of the RuST, this being the most important tract for the control of voluntary movement in the dog and cat. In human biped, this tract is involved in activities such as swimming with the superior limbs.

In dogs, only 10 to 20% of descendant UMN tract needs to be intact, after severe spinal cord injury, for there to be limb movement (Thomson & Hatin, 2012).

The VST tract stimulates the extensor muscles ipsilaterally and inhibits extensor muscular tonus contralaterally (Thomson & Hatin, 2012).

The medullar RST is responsible for the inhibition of the gamma motor neuron.

In the biped human, pure pyramidal lesions do not result in spasticity, because a large portion of voluntary movement relies on extrapyramidal pathways (Ropper, Samuels & Klein, 2014), among which are the spinal corticoreticular pathways.

The UMN lesions in the human biped usually cause flexed like postures and pronated superior limbs postures, as well as extended and abducted inferior limbs. Spasticity depends on the increase of resistance to the passive stretching of the muscles. If a lesion involves the CST, the RST is usually involved as well (Ropper, Samuels & Klein, 2014). The greatest indicator of upper UMN in the human biped is the Babinski sign, described in 1896.

Electrostimulation to facilitate locomotion and autonomous rise

In the human biped there is evidence that, after spinal cord injury leading to paraplegia, electrostimulation, in order to stimulate the sensory input of limbs, associated with a locomotor training of several weeks, is enough to achieve an active standing posture, enabling the patients to support 100% of their body weight. The presentation of voluntary movements may occur, but only when the electromiostimulation is applied. The position of the electrodes is important and should always be in anode - cathode orientation.

Human biped with quadruped animals study comparison

The quadruped animal model most used in experimental studies is the rat, in which it is caused transection of the spinal cord, leading to paralysis. Unilateral lesions of the cervical spinal cord are preferentially used as spinal cord injury model in the human biped (Nout *et al.*, 2012). This is due to the fact that the most common clinical lesions in the human are cervical, being of primary interest for the study of the superior limbs and hands, due to the anatomical and behaviour resemblance that the rat and the human share (Nout *et al.*, 2012, Gad *et al.,* 2013).

Although anatomically similar, there are differences in the number, location and termination of the motor pathways. The fine motor control present in the human and primates is achieved through the CST, whilst in the rat, the same fine motor control is achieved by the RuST, which is vestigial in the human biped (Nout *et al.*, 2012). Other important differences are the effects of the secondary lesion and the nerve regeneration capability, that in the rat is millimetres and in the primate is centimetres.

Considering the above data, several studies look for the *Macaca mullata* as a preferential animal model, to which is induced, experimentally, spinal cord transection at C7 level (Nout *et al.*, 2012).

The primate rehabilitation program consists of: 30 minutes of assisted ground locomotion, 5 times per week; 20 minutes of treadmill training, 2 times per week; and 30 minutes of rehabilitation wheelchair training, during a 24 week period. All patients show voluntary movement after 15 days of spinal cord transection, with significant evolution after 3 to 8 weeks.

In primates, 87% of CST descends dorsolaterally by the spinal cord and contralaterally to the cerebral hemisphere of origin; the remaining 11% descend ipsilaterally to the hemisphere of origin. In the rat, however, 96-98% of the descendant axons of the CST decussate at medullar pyramids level, a very important fact concerning neural plasticity (Nout *et al.*, 2012).

The remodelling of neural circuits is the result of neuronal plasticity, and it may occur at different sites of the central nervous system, allowing the restoration of movement after locomotor training, and is therefore indicative of neural reorganization, occurring simultaneously in supraspinal and spinal cord circuitry.

The CST is a pathway between the motor cortex and the spinal cord, and even if their neurons are not necessary for there to be locomotion, they have an important modulator role in the cat's locomotion. This modulation combines inputs originated from CPG and the afferent feedback reflex, allowing coordination between the limbs (Harkema *et al.*, 2012; Knikou, 2012).

The modulation of the CST allows adjusting movement when an obstacle emerges in the placement of the limbs in the correct position.

Relation between degenerative intervertebral disc disease (DIVDD) in the dog and in the human

The thoracolumbar discal hernias in dogs occur spontaneously, similar to acute injuries of the spinal cord in humans.

Most histopathological lesions observed in dog's

DIVDD may be observed in the traumatic myelopathy of the human. Typically, these lesions translate into intraparenchymal haemorrhage on the surface of marrow necrosis with cystic massive evolution and compression, representing 79% of spinal cord injuries present in the human biped (Nout *et al.*, 2012).

Neural injury and demyelination are common in both human and dog, as well as neural necrosis and neutrophilic infiltration, and it can be observed after weeks to months.

In human, 61.2% of hernias occur in the cervical region, followed by hernias in the thoracic (25.2%) and lumbosacral region (13.6%), while in the dog, 83.6% of hernias occur in the thoracolumbar region (Nout *et al.*, 2012).

The primary lesion in both species occurs under the form of compression/contusion to the ventral area of the spinal cord (Levine *et al.*, 2011).

In 2001, Olby and colleagues created a locomotor rating scale for dogs with spinal cord injury, the BBB, and used it in rats. More recently, the modified Frankel scale has arisen, which is based on the evolution of gait, postural reactions and nociception.

The presence of hyperintensity on T2 in a presurgical status results in a poor prognosis regarding functional recovery after surgery.

The CST is far more important to ambulatory function in the human than it is in the dog, due to this fact, spinal shock is transient in dogs with DIVDD, when compared to the human.

Discussion

During the study, it was found that the result of neurorehabilitation is potentiated by neuroplasticity, both supraspinal and medullar (Thompson & Walpaw, 2014).

Following a constant discussion about the origin of the movement, it can be stated that there are two main lines of thought (Chang, 2014; Gad *et al.*, 2012; Garcia *et al.*, 2015). In one hand, the line that holds that supraspinal inputs are needed to generate involuntary movement, and on the other hand the line that claims that the spinal cord contains internal circuitry of CPG that allows a fictive locomotion (Chang, 2014).

Regardless of the line of thought, there must be coordination between the forelimbs and hind limbs (Cazalets & Butrand, 2000; Nathan, Smith & Deacor, 1996), as well as memorization of this coordination (Nielsen, *et al.*, 2015; Zhong *et al.*, 2012).

Thus, neurorehabilitation must take into account the intrinsic properties of the nervous system, neuroplasticity and functionality, with the latter comprising the management of pain, thereby turning neurorehabilitation into FNR.

The importance of FNR surpasses the properties of the nervous system, by the fact that neuroplasticity depends on the accomplishment of the rehabilitation methods described throughout the article, these being epidural, transcutaneous or intraspinal electrical stimulation, pharmacological means and locomotor training, which, when combined, have greater results regarding voluntary or fictive locomotion (Gad *et al.*, 2012; Harkema *et al.*, 2012; Lavron *et al.*, 2015; Musienko *et al.*, 2012; Nandra *et al.*, 2011; Roy & Edgerton, 2012; Roy, Harkema & Edgerton, 2012; Solopova *et al.*, 2015; Thompson & Walpaw, 2015).

The FNR should also be based on neuromodulation, exploiting all circuits of interneurons and motor neurons, and increasing their depolarization.

It would be important to clarify the descending spinal tracts that stimulate excitatory post-synaptic potential (Knikou, 2012) in all animal models used for comparative study with the human.

It is known that the primate is the animal model with most resemblance to the human. In the primate, 11% of axons of the descending pathways of the CST descend the spinal cord ipsilaterally to the hemisphere of origin, which may be compared with the 10% that the dog exhibits (Ropper, Samuels &

Klein, 2014). These 11% of axons of the CST that descend the spinal cord ipsilaterally in primate and 10% in the dog, are extremely important in FNR, as it is through them that neuromodulation and neuroplasticity are achieved. Apart from that, when the CST is damaged in the human, it has to resort to extrapyramidal tracts, which are vestigial in the human, to recover, making studies in the dog and cat essential for the study of the human.

In relation to the dog, it presents a uniqueness: the dog only requires 10 to 20% of UMN pathways to achieve a normal locomotion (Thomson & Hatin, 2012), making its FNR a reference to the human.

The cat also presents an interesting particularity, it is considered an extrapyramidal animal model, but it needs the integrity of some of the CST pathways so that modulation and coordination may occur, one aspect that is similar to human (Duysens & Crommert, 1998; Knikou, 2012).

As for the rat, the control of fine motor movement is achieved through the RuST, while in man this is achieved through the CST.

A relation exists between the DIVDD in the human and the dog. DIVDD in human and dogs present similarities as to clinical presentation, diagnosis, surgical approach (Bergknut *et al.*, 2011) and FNR.

Conclusion

With this article we can conclude that, due to neurophysiology and neuroanatomy, FNR in human biped and quadruped can be similar, and its adaptation may be reciprocal. We know that, for both, locomotor training should begin as soon as possible and with the greatest intensity within the limitations of the disease (Ditunno *et al.*, 2012; Duffell & Mirbagheri, 2015; Hettlich & Levine, 2012; Kim *et al.*, 2014; Oosterhuis *et al.*, 2013; Takao *et al.*, 2015).

The article suggests utilizing the cat and dog as an animal model, because in both, if the spinal injury is complete, after a few days of locomotor training applied after spinal cord section, the fictive locomotion is achieved and therefore also a possibility of independence (Gad *et al.*, 2012; Musienko *et al.*, 2012; Siegel *et al.*, 1979), in addition to the similarities among the degenerative diseases of man and dog.

The UMN descending pathways can be correlated between human, dog and cat, and hence also the locomotor training exercises. In the rat, since it presents a spinal cord of millimetres in diameter, the power for regeneration is enhanced, potentially facilitating the onset of coordinated locomotion or fictive locomotion.

We can conclude that, to attain quality of life, locomotor training is essential, as is the timing of its beginning, and that future studies can be performed with dog and cat model as research model. Further studies will be required, perhaps even the formation of a robotic model for these animals, in order to understand, by evidence, the human biped and apply this model to him.

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