Human Locomotion and the Motor Cortex

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Drive to the Motoneuron and the Role of Afferent Input

PhD Thesis by

Abraham T. Zuur

Center for Sensory-Motor Interaction (SMI),
Department of Health Science and Technology,
Aalborg University, Aalborg, Denmark

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Preface

This dissertation is based on work carried out between February 2004 and July 2006, and between November 2007 and August 2008 at the Department of Neuroscience and Pharmacology and the Department of Exercise and Sport Sciences at the University of Copenhagen as well as at the Centre for Sensory-Motor Interaction (SMI) at Aalborg University. The finalisation of the project was postponed due to the completion of my studies at medical school.

The core of the thesis is consisting of five original research papers. The chapters surrounding these papers provide background for the role of the motor cortex in human walking and hopping. It will also raise the question whether walking should be termed automated, or voluntary. The results of the papers in brief will be discussed in the final chapter.

Abraham Theodoor Zuur
Enschede, 2013

Abstract

Human walking displays an impressive precision and the ability to adapt to different terrains. It is suggested that both spinal as well as supra-spinal structures play an important role in this rhythmic task. The current thesis focuses on the role the motor cortex plays in this task. Although there are experimental findings and clinical observations suggesting that one of the supraspinal structures involved in walking is the motor cortex, it is not generally accepted that the motor cortex is of major importance in human locomotion. The motor cortex is generally considered to be important in voluntary movement and the choice to term walking as non-voluntary movement may be more than just semantically important and this matter is discussed in the thesis.

The thesis includes five original research papers which show that output from the motor cortex is integrated with contributions from spinal structures in rhythmic tasks such as walking and hopping. In study I it is shown how the motor cortex contributes to motoneuronal drive in conjunction with sensory feedback mediated by spinal reflex loops. The integration between afferent feedback and motor cortex is further displayed in study II, in which we show that afferent input may relay to corticospinal neurons from where it is fed back to the muscle and may produce a large functional directed response during walking. Study II thereby displays a role for the motor cortex in error correction during walking. Study III shows not only that afferent feedback from agonist muscles is relayed to corticospinal neurons during walking but also that feedback from the antagonist is relayed to the motor cortex where signals from both muscles increase the excitability of the motor cortex. This organisation is somewhat reversed from the organisation of antagonist afferent input to the spinal cord, but it may be hypothesised that both spinal and supra-spinal structures contribute to a balanced response to a perturbation. The motor cortex also plays a role during normal, unperturbed walking. In study IV we show that output from the motor cortex may be suppressed during walking and standing by exciting intracortical inhibitory interneurons using subthreshold transcranial magnetic stimulation. The results may be explained by the suggestion that there is less corticospinal output during walking. Alternatively, it may be suggested that it is more difficult to stop the corticospinal neurons or motoneurons from firing during walking. The final study showed that muscle activity can still be suppressed during a dynamic contraction during sitting and it also suggests that the observed effects cannot be unambiguously related to changes in corticospinal output.

In conclusion, the studies in the thesis further confirm a role for the primary motor cortex in driving the muscle during rhythmic tasks like walking and hopping. It shows a role for the motor cortex in mediating afferent feedback to both agonists as well as antagonists, underlining the integrative nature of the neural system. Indirect measurements of the ability of intracortical inhibitory neurons to suppress corticospinal neurons suggest that the motor cortex is involved in both walking and standing, but that the control is very different.

Dansk resumé (Abstract in Danish)

Det menneskelig gangmønster viser imponerende præcision og evne til at tilpasse sig til forskelligt terræn. Det er blevet foreslået at både spinale og supraspinale strukturer spiller en vigtige rolle i denne rytmiske opgave. Denne afhandling er centreret om hjernebarkens rolle ved gang og hop. Selv om eksperimentelle resultater og kliniske observationer antyder at hjernebarken er en af de supraspinale strukturer som er involveret i gang, er det ikke generelt accepteret at hjernebarken er af stor betydning i den menneskelige gang. Den motoriske hjernebark anses generelt for at være vigtig i voluntære bevægelse og en beslutning om at beskrive gang som en ikke- voluntære bevægelse, kan være mere end bare et semantisk vigtigt spørgsmål, hvilket også tages op i afhandlingen.

Specialet omfatter fem originale forskningsartikler, som viser, at output fra den motoriske hjernebark er integreret med bidrag fra spinale strukturer i rytmiske opgaver som gang og hop. Studie I påviser, hvordan den motoriske hjernebark bidrager til at styre motoneuroner sammen med sensorisk feedback medieret af spinale reflekser. Integrationen mellem afferent feedback og hjernebarken er yderligere vist i studie II, hvor vi viser, at afferente input overføres til corticospinal neuroner, hvorfra det føres tilbage til musklen og producerer en stor funktionelt rettet reaktion i gangmønstret. Derved viser study II at den motoriske hjernebark spiller en rolle i fejlkorrektion under gang. Studie III viser, at ikke kun afferent feedback fra agonist muskler videresendes til corticospinal neuroner under gang, men at også feedback fra antagonisten videresendes til den motoriske hjernebark, hvor signaler fra begge muskler øger ophidselse af den motoriske hjernebark. Denne organisation er på en måde modsat af organiseringen af antagonist afferent input til rygmarven, men det kan foreslås at både spinal og supra-spinal strukturer tilsammen bidrager til en afbalanceret respons på en forstyrelse. Den motoriske hjernebarke spiller også en rolle under normal uforstyrret gang. I studie IV viser vi, at output fra den motoriske hjernebark kan undertrykkes ved sub-tærskel transkraniel magnetisk stimulation under gang og i ståendende stilling. Resultaterne kan forklares ud fra et forslag om, at der er mindre corticospinal output under gang i sammenligning med stående stilling. Alternativt kan det foreslås, at det er vanskeligere at hindre de corticospinal neuroner eller motorneuroner i at fyre under gang. Den sidste undersøgelse viste, at muskel aktivitet dog kan undertrykkes ved hjælp af sub-tærskel magnetisk stimulation under en dynamisk muskelkontraktion og resultaterne indikerer, at de observerede effekter i studie IV og V ikke entydigt kan relateres til ændringer i corticospinal output.

Undersøgelserne i specialet bekræfter at hjernebarken har en rolle i forhold til at styre musklen under rytmiske opgaver som at gå og hoppe. De viser at den motoriske hjernebark spiller en rolle i mediering af afferent feedback til både agonister og antagonister, hvilket understreger integrerende karakter af det neurale system. Indirekte målinger af intracortical hæmmende neuroners evne til at undertrykke corticospinal neuroner antyder, at det hjernebarken er involveret i både det at gå og stå, men at den kontrollen muligvis er meget forskellig

Fryske gearfetting (Abstract in Frisian)

It gean fan de minske lit in sekuerens sjen dy't yndruk makket. Boppedat kinne we op hiel ferskillende wizen rinne. Der wurdt tocht dat senuwstruktueren op en boppe it nivo fan it rêchpiid dêryn in taak ha. Yn dizze teze giet it benammen om de rol fan de bast fan de harsens by it rinnen of springen. Ek al jouwe eksperiminten en klinyske observaasjes oanwizings dat de harsenbast ien fan 'e wichtichste boppe-rêchpiidske struktueren foar it rinnen is, wurdt dat net oeral erkend. Wol wurdt fakernôch oannommen dat de harsenbast wichtich is by frijwillige bewegings. Dêrom is de kar om rinnen te beneamen as net-frijwillich mear as inkeld wurdboarterij.

Yn dizze teze sitte fiif orizjinele ûndersyks-artikelen dy't sjen litte dat sinjalen út de harsenbast harren gearfoegje mei sinjalen út oare senuwstruktueren om sa in ritmyske beweging oan te stjoeren. Stúdzje I lit sjen hoe't de harsenbast it motoneuron oanstjoert en hoe't dat yntegrearre is mei sensoaryske ynformaasje út de skonken. It gearfoegjen fan afferinte sinjalen en sinjalen út de harsenbast is ek oantoand yn stúdzje II. Yn dy stúdzje litte we sjen hoe't afferinte sinjalen nei de harsenbast geane en fan dêrút soargje foar in grutte reaksje yn de spieren fan de skonken. Stúdzje II lit sadwaande sjen hoe't de harsenbast soarget foar korreksje fan ôfwikings fan it foarnommen ferrin fan de beweging. Stúdzje III lit sjen dat yn de harsenbast ynformaasje fan sawol de agonist as de antagonist oankomt en dat beide kearen de saneamde eksabiliteit tanimt. Dizze organisaasje is likernôch it omkearde fan de organisaasje fan antagonistyske afferinte input nei it rêchpiid, mar wy kinne de hypoteze pleatse dat spinale en supra-spinale struktueren gearwurkje oan in balansearre reaksje nei in fersteuring. De harsenbast spilet ek in rol yn it gewoane, ûnfersteurbere rinnen oer in sljochte ûndergrûn. Sa litte wy yn stúdzje IV sjen dat de output fan de harsenbast ûnderdrukt wurde kin troch remjende yntrakortikale senuwen te eksitearen mei sub-threshold transkraniele magnetyske stimulaasje (TMS). De resultaten kinne útlein wurde troch de suggestje dat der ûnder it rinnen minder output is út de harsenbast as by it stean. Dochs kin it ek útlein wurde mei de suggestje dat it ûnder it rinnen dreger is om de aktiviteit fan in kortikospinale senuw te stopjen. De lêste stúdzje lit sjen dat men mei sub-threshold TMS ek spieraktiviteit ûnderdrukke kin by in dynamysk gearlûken fan de spier en dat ûnderdrukking fan de spieraktiviteit net altiten hielendal gear liket te hingjen mei de poarsje aktiviteit dy't der út de harsenbast komt.

De stúdzjes yn dizze teze befêstigje in rol foar de harsenbast yn ritmyske taken lykas rinne en springe. It lit in rol foar de harsenbast sjen yn it ferwurkjen fan sinjalen fan agonist en antagonist en ûnderstreekje sa it gearwurkjen yn it senuwsysteem. Yndirekte mjittingen nei

hoe maklik remjende senuwen spieraktiviteit ûnderdrukke kinne, litte sjen dat de harsenbast belutsen is by sawol rinnen as stean, mar dat dy ferskillende oanstjoering lykje te hawwen.

Contents

Abbreviations

aMT – active motor threshold
BOLD – Blood Oxygen Level Dependent
CMEP – Cervicomedullary evoked potentials
CNS – Central nervous system
CPG – Central pattern generator
CPN – Common peroneal nerve
CST – Corticospinal tract
DF – Dorsiflexion
EMG – Electromyography
FSR – Functional stretch reflex
GABA – γ-amino butyric acid
GM – Gastrocnemius muscle
HS – Heel strike
IPSP – inhibitory post synaptic potentials
LLR – Long latency stretch reflex
MEP – Motor evoked potential. [*If not otherwise specified this is a TMS-evoked MEP.*]
MRI – Magnetic resonance imaging
MSO – Maximum stimulator output
NIRS – Near infrared spectroscopy
PET – Positron emission tomography
PF – Plantar flexion
PIC – Persistent inward currents
SCI – spinal cord injury
SICI – Short-interval intracortical inhibition
SOL – Soleus muscle
TA – Tibialis Anterior muscle
TES – Transcranial electrical stimulation
TMS – Transcranial magnetic stimulation
TMS_{ES} – TMS-evoked EMG suppression
SPECT – Single positron emission computer tomography

List of original papers

Study I
Zuur AT, Lundbye-Jensen J, Leukel C, Taube W, Grey MJ, Gollhofer A, Nielsen JB, & Gruber M (2010). Contribution of afferent feedback and descending drive to human hopping, 3. *J Physiol* 588, 799-807.

Study II
Zuur AT, Christensen MS, Sinkjaer T, Grey MJ, & Nielsen JB (2009). Tibialis anterior stretch reflex in early stance is suppressed by repetitive transcranial magnetic stimulation. *J Physiol* **587**, 1669-1676.

Study III
Zuur AT, Sinkjaer T, Nielsen JB, Grey MJ (*unpublised*). Stretch induced afferent input affects cortical and subcortical pathways to soleus in different phases of the step-cycle.

Study IV
Zuur AT, Perez MA, Sinkjaer T, Nielsen JB & Grey MJ (*unpublished*). Intracortical inhibition during human walking and standing.

Study V
Zuur AT, Perez MA, Sinkjaer T, Nielsen JB & Grey MJ (*unpublished*). Intracortical inhibition during force modulation in the soleus muscle.

Thesis at a glance

	Question	Methods	Answer
I	a. Is the first peak during hopping of a reflex origin? b. Does the motor cortex contribute to the EMG during this peak?	19 healthy volunteers, hopping, TMS_{ES}, moving platform	a. Yes, the first peak is of reflex origin b. Yes, the motor cortex contributes to the EMG during this peak, showing that afferent feedback and descending input work together in concert.
II	Is the cortex mediating the large reflex elicited in mid-swing during standing?	30 healthy volunteers, walking, sitting, sudden ankle plantar flexion perturbations, rTMS	Yes, the later part of the reflex is mediated by a transcortical pathway.
III	a. Does afferent information from the antagonist muscle cause corticospinal facilitation? b. If it does, what is the origin of this facilitation?	16 healthy volunteers, sudden, walking, sudden DF/PF ankle perturbations, TMS, TES	a. Yes, there is corticospinal facilitation after afferent information is elicited from the antagonist during walking. b. The afferent feedback generated after DF in mid-stance is relayed to subcortical structures, while afferent feedback generated after PF in mid-swing is relayed to the motor cortex.
IV	a. How do TMS_{ES} and SICI change during walking and standing, and how is this related to difference in corticospinal drive? b. Do both methods employ a common neurontransmittor?	14 healthy volunteers, walking, standing, TMS_{ES}, SICI, Diazepam, Baclofen	a1. SICI is low during both standing and walking possibly reflecting the need to decrease inhibition to allow corticospinal neurons to fire. a2. TMS_{ES} is less during walking than during standing, reflecting less corticospinal drive during walking or that it is more difficult to inhibit the firing of corticospinal neurons during walking. b. Both methods are suggested to employ a similar pathway.
V	How do intracortical inhibitory pathways modulate during force modulation? Can this modulation be related to corticospinal output?	26 healthy volunteers, ramp-and-hold profile while sitting, SICI, TMS_{ES}.	Decreases in SICI and are not always accompanied by a change in TMS_{ES} and vice versa. Differential changes in TMS_{ES} and SICI cannot unambiguously be related to corticospinal output.

1 Introduction

Walking and hopping are locomotor tasks which display a strong rhythmicity. Despite the large forces needed for propulsion and weight bearing, the movements are very precise (Winter, 1983). The neural control of these rhythmic tasks is, to a large extent, still unknown and the role of the motor cortex in these tasks is also not fully understood.

Studies in the beginning of the previous century showed that in cats supra-spinal structures were not necessary to produce a basic locomotor pattern and that the structures generating a locomotor-like pattern are entirely contained within the spinal cord (Brown, 1911). Given the remarkable ability of the separated spinal cord of many mammals to display locomotor patterns, the impact of acquired brain injury on human walking, such as a stroke, is striking (Perry *et al.*, 1995;Lamontagne *et al.*, 2007). This clinical observation is in line with the suggestion that supra-spinal control may play an important role in human locomotion. One of the supra-spinal structures which may play an important role in the control of human walking is the motor cortex which is the subject of this thesis.

1.1 Aim of the thesis

In the papers of this thesis we studied the role the motor cortex plays in controlling locomotion. Locomotion includes walking which is the main theme of the thesis, but a study on hopping is also included, since hopping is also a rhythmic bipedal movement in which spinal reflexes are suggested to play a role and in which the motor cortex may well contribute.

In short, the aim of this thesis is to elucidate if the motor cortex plays a role in rhythmic tasks such as walking and hopping, including the integration of sensory input to the motor cortex and the integration of cortical output with spinal structures. This aim can be sub-divided into the aims of the individual studies. While it is shown that the motor cortex contributes to the drive to the motoneuron during walking, it is unknown if this also plays a role in hopping. Hopping is a task in which reflexes are suggested to play an important role and consequently it may be suggested that the motor cortex plays a less important role. Therefore, the goal of study I was to elucidate whether reflexes really do play an important role during the first peak of muscle activity observed after ground contact during hopping. After this was confirmed we pursued the second goal, which was to reveal whether the motor cortex also plays a role at this stage of the rhythmic task.

In the subsequent three studies we studied the role of the motor cortex in walking. One of the possible roles of the motor cortex is to mediate a transcortical reflex. In study II the aim was to elucidate whether the motor cortex mediates the large response in the tibialis anterior muscle which is observed after a plantar flexion perturbation during standing.

Recently more suggestions have been put forward that the motor cortex not only receives afferent information from the homonymous muscle, but also receives input from antagonists. Therefore, in study III our goal was to reveal whether afferent input from both agonist and antagonist muscle also projects to the motor cortex during walking.

In Study IV we evaluated the effect of exciting intracortical inhibitory interneurons during walking and standing. Previous studies have suggested that a decreased excitability of intracortical inhibitory interneurons may reflect the functional necessity to decrease intracortical inhibition in order to let corticospinal neurons fire. The aim of this study was to see whether such a reduction was also present during walking. Evaluations were undertaken to ascertain whether intracortical inhibition was different between walking and standing. The difference found between walking in standing may reflect differences in the corticospinal control of both tasks.

In Study V we evaluated the effect of exciting intracortical inhibitory interneurons during a static and dynamic task. We tested the hypothesis that the effect of exciting intracortical inhibitory interneurons is dependent on corticospinal drive. The findings in this study are related to the findings Study IV in which some of the same methods are used.

1.2 Outline of the thesis

A thesis on the role of the sensorimotor cortex in locomotion would not be complete without discussing other structures which contribute to the recruitment of motoneurons during locomotion, including afferent feedback, a possible spinal pattern generator, other descending pathways and the intrinsic properties of the motoneuron. These are described in chapter 2.

Chapter 3 describes experimental and clinical evidence from literature on the role of the motor cortex in locomotion. The study focuses on human walking, but evidence from animal experiments will be also discussed.

Chapter 4 describes the relation between voluntary, motor cortex and walking. Walking has often been separated from a *voluntary* contraction. It may well be that this separation is

not purely semantic, and that it influences the way we think about the involvement of the motor cortex in walking. After all, the motor cortex has traditionally been considered the domain of voluntary movement.

The final chapter summarises the findings from the studies and finishes with an overall conclusion. Figure 1 displays how the different chapters and studies in the thesis relate to each other.

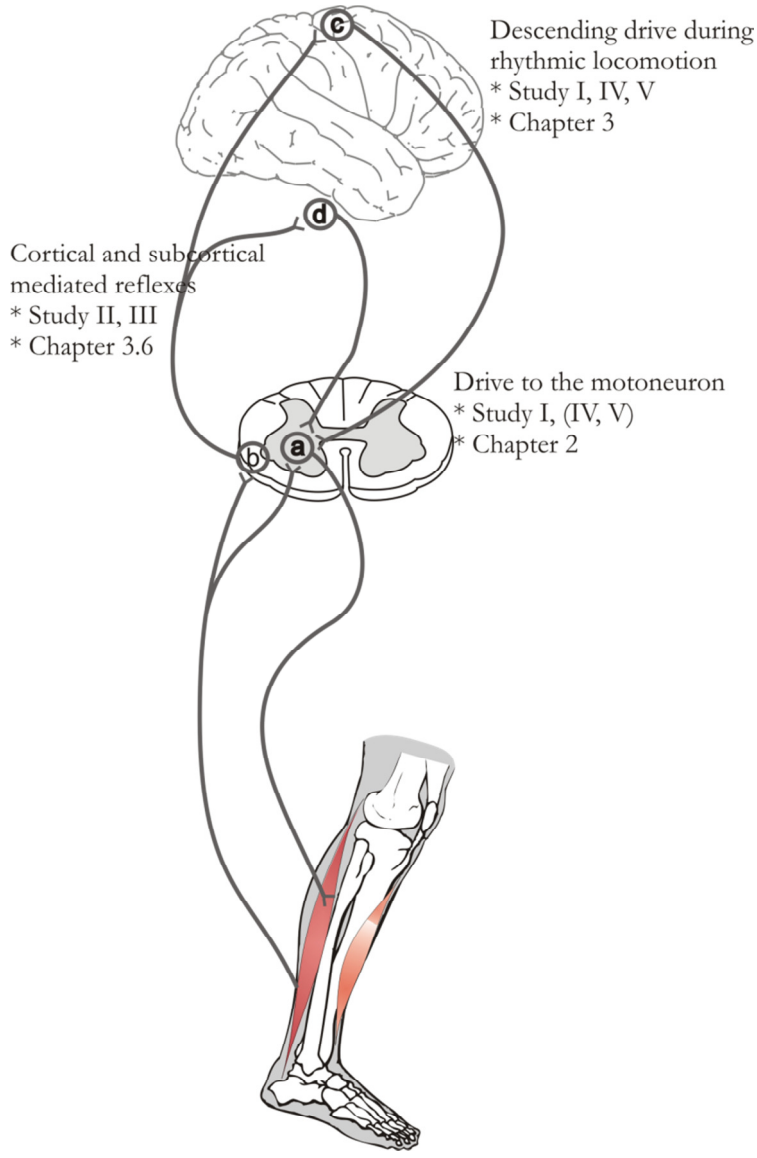

Figure 1, Schematic representing the neural pathways studied in the thesis and referring to the studies and chapters of the thesis. a) is the motoneuron b) an interneuron relaying afferent data to cortical and subcortical structures. c) corticospinal neuron, d) subcortical neuron.

2 Sources of drive to the motoneuron during locomotion

The motoneuron may be considered the final common pathway in the neuromuscular control of any movement, including hopping and walking. What in turn produces recruitment of the motoneuron to produce a (cyclic) movement is a central but to a large extent unanswered question in motor control research. A thesis on the role of the sensorimotor cortex in locomotion would not be complete without discussing sources other than those of corticospinal origin. Contributions from sources other than the corticospinal tract are not only important because they may provide (part of the) drive during locomotion, but also because they are likely to be highly integrated with corticospinal pathways and may act in concert with these pathways to produce the movement. Such integration may imply that output from one structure may be greatly modulated by input from another structure. Edgerton phrases this nicely when he says "the spinal cord functions as part of the brain, not as its servant" (Lemon, 2008).

Although the chapter is divided into subchapters on the different contributions, the neuro-anatomic borders between the different structures may not be as clearly defined as the subchapters suggest.

Box 1: Headless chicken

In 1945 a farmer from Colorado was send by his wife to slaughter a chicken. He went out to find the chicken and decapitated the animal but incidentally cut high on the neck and left the brainstem intact. Most vital functions therefore remained and the chicken survived for 1.5 year. Despite missing most of his head, the bird was still able to walk. He became a big attraction and a yearly festival is held in remembrance of the chicken.

2.1 Spinal central pattern generator (CPG)

It was probably noticed early in the history of humankind that shortly after a chicken was decapitated, it was still able to walk (see box 1 for an exceptional case), suggesting that the brain is not necessary for walking. Early observations in a laboratory setting showed stepping-like behaviour after a complete transection of the spinal cord in dogs (Goltz &

Freusberg, 1874). To confirm that this stepping-like behaviour is not produced by afferent input, Graham Brown (1911) cut the dorsal roots so that essentially all sensory input to the spinal cord is removed. Soon after the transection of the spinal roots, the cats showed rhythmic activity in the ankle flexors and extensors and thereby confirmed an intrinsic ability of the spinal cord to generate such rhythms. Such a rhythm-generating structure is termed a central pattern generator and is found in many other species (Grillner, 1975). In animals with lesions to the spinal cord and with peripheral afferents intact, the ability to walk is well preserved including the weight support of the hindquarters and proper plantar foot placement (Rossignol *et al.*, 1996;Barbeau & Rossignol, 1987). Such weight-bearing ability has not been observed in humans with a clinically complete transection of the spinal cord, although involuntary rhythmic activity has been observed after stimulation of the flexor reflexes (Holmes, 1915;Kuhn, 1950;Bussel *et al.*, 1988;Calancie, 2006). Such locomotor-like rhythms could also be evoked in patients with a clinical complete spinal cord transection by non-patterned epidural stimulation (Dimitrijevic *et al.*, 1998). For the interpretation of these studies, it is important to note that none of the studies provides anatomical evidence that the spinal cord lesions were indeed complete. Although the studies are often cited to suggest that the human spinal cord is able to produce rhythmic activity by itself, supra-spinal influence in these studies cannot be excluded.

2.2 Supra-spinal input

Section 2.1 describes how rhythmic movements are possible without descending input. However, there is good evidence that drive from descending pathways contributes importantly to locomotion. The main descending pathways can be divided into three groups, including the corticospinal tract (CST) and two groups (A and B) descending from the brainstem (Kuypers, 1981;see also Rothwell, 1986). The tracts of group A originate from the brainstem and comprise the insterstitiospinal, tectospinal, vestibulospinal and part of the reticulospinal tract. Since these neurons make many collateral connections, they seem to be very suitable for synergistic activation of a large number of muscles. The observation that cats with a transection of the vestibulo- and the reticulospinal show major locomotor and postural defects may suggest that these more ventral pathways play a role in walking (Brustein & Rossignol, 1998). The more dorsolateral group B consists of a rubrospinal pathway and the crossed reticulospinal tract from the pontine lateral tegmental regions. These connections have limited collaterals and are thought to project mainly to distal muscles. The importance of this group of connections may have limited importance in walking. In a group of four males in which the anterior part of the cord was divided, but which left the corticospinal tract intact, hardly any motor deficits were seen(Nathan, 1994). Also walking was virtually unaffected.

The final group is the corticospinal tract which seems generally more important in humans than in cats (Lemon & Griffiths, 2005). The neurons from the corticospinal tract originate from the motor cortex and run through the medullary pyramids, forming most of the pyramidal tract. Given that the number of muscles in human and other mammals is comparable, it is remarkable that the human pyramidal tract consists of around 1 000 000 in comparison to 800 000 in chimpanzees, 400 000 in macaque monkeys and 186 000 cats (Rothwell, 1986). There is increasing evidence that the corticospinal tract plays an important role in locomotion (see also chapter 3). However, it is also suggested that walking is possible with an almost fully transected spinal cord. Nathan *et al.*(1994) describe a patient who underwent bilateral posterolateral cordotemy of the spinal cord at a level of T5, which was shown *post-mortem* to leave only 10-15% of the corticospinal fibres on one side intact. Despite the large incision and the large damage to the corticospinal tract, the patient relearned to walk after the first month, but his walking was impeded by clonus and flexor spasms(Nathan, 1994). In contrast, Wiesendanger (1969) mentioned a subject who had a tumor which had destroyed most of the brain stem except the pyramidal tract. Despite this, the patient was capable of performing normal voluntary movements. Unfortunately, it is unclear whether "voluntary movements" also included walking. Further support for the suggestion that the corticospinal tract contributes to locomotion is provided in a recent study from Barthélemy *et al.*(2010). They show that electrophysiological measures reflecting the integrity of the corticospinal tract correlates with the amount of drop foot in patients with a spinal cord injury (SCI). They also show that motor evoked potentials (MEPs) elicited by TMS at rest have a good correlation with gait speed.

2.3 Afferent input

The human neuromuscular system uses sensory information in several ways (Nielsen & Sinkjaer, 2002). First, sensory information may be used to inform the CNS about errors in the execution of the movement, so that the current movement can be adapted. Second, this sensory information can also be used to update future movements. Third, sensory information helps internal commands in the driving of output neurones as part of all normal voluntary movements.

In studies II and III, we applied a mechanical perturbation during walking and thereby provided the CNS with an error signal. This in turn produces functionally directed reflex responses. Also in study I we provide the system with an error signal when we suddenly move the platform up in between two hops. In these studies we recognise the words of Sir

Sherrington whose pioneering work in reflex physiology brought the term into common scientific research. He wrote:

"... all parts of the nervous system are working together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts, and it is a system certainly never absolutely at rest. But the simple reflex is a convenient, if not probable, fiction. Reflexes are of various degrees of complexity, and it is helpful in analysing complex reflexes to separate from them reflexes which we may consider apart and therefore treat as though they were simple reflexes"
(Sherrington, 1906).

Indeed, in study I we investigated whether the motor cortex also plays a role during the time of the stretch reflex, hypothesising that the motor cortex may contribute to drive the motoneuron in addition to a contribtution from afferent input. In study II & III we asked ourselves whether the motor cortex is involved in mediating stretch reflexes during walking.

Box 2: A daily marathon

In 1971, Ian Waterman a 17-year old apprentice butcher contracted what first appeared like a normal flu. However, over the next few days his condition got worse, and over the course of a few days he lost a large part of his skin afferents and proprioception, probably due to an auto-immune process. This made the control of any movement including walking very difficult and it was only thanks to great perseverance that he relearned to walk. His pattern of walking differs from a normal one in an apparent way, but it shows that walking without afferent feedback is possible thanks to compensatory strategies. Nonetheless, these compensatory strategies require the same energy and will power as would be needed to run a marathon every day of the year (Cole, 1995).

While the role of afferent feedback in error correction is recognised to be important, it also has an important role during unperturbed locomotion where afferent feedback contributes to the ongoing muscle activity (for review see Lam & Pearson, 2002; Nielsen & Sinkjaer, 2002). Cat-experiments which are referred to as "foot-in-hole" experiments showed a reduction in extensor activity when there was unexpected loss in ground support (Gorassini *et al.*, 1994). Similarly, experiments in humans showed that unloading of the ankle extensors by sudden plantar flexion decreases the ongoing muscle activity by 50% in early and mid-stance (Sinkjaer *et al.*, 2000). This drop may not be explained by reciprocal inhibition since the drop in muscle activity remains after the common peroneal nerve (CPN) has been blocked with local anaesthetics, thereby blocking afferents from the ankle dorsiflexors. The importance of afferent input may also be appreciated in people with a neurological illness which destroys part of their sensation (box 2). In study I we

transiently remove the expected afferent feedback during hopping by lowering a platform. Differences and similarities between this study in hopping and the study in walking (Sinkjaer *et al.*, 2000) are discussed in the discussion in section 5.3.

2.4 Intrinsic properties of the motoneuron

The sections above describe how different sources provide input to the motoneuron. The effect of such input on firing frequency is largely dependent on properties of the motoneuron itself. These intrinsic properties may contribute to a highly non-linear behaviour and this often complicates interpretation of results and therefore cannot be disregarded (as is also discussed in Study IV and V). Intrinsic properties of the motoneuron determine amongst other things the recruitment order: i.e. the order in which motor units are recruited during increasing strength of contractions. Different neurons may have different thresholds before synaptic input causes recruitment in the task (Gustafsson & Pinter, 1984;Zengel *et al.*, 1985). Other properties, like the maximum firing frequency may be dependent on the amount hyperpolarisation that follows recruitment (Kernell, 1965). One other example of an intrinsic property of the motoneurons which is also brought up in Study IV and V as one of the possible and partial explanations of the results, are persistent inward currents (PICs). The PIC may be generated by non-inactivating voltage depending Ca^{2+}-channels, and it may cause self-sustained firing in the absence of synaptic input (Schwindt & Crill, 1980). Such intrinsic activation has also been suggested to play a role in human motor neurons (Gorassini *et al.*, 2002a; Gorassini *et al.*, 2002b)

Finally, although it is not purely dependent on intrinsic properties of the motoneuron, it should be noted that the effect of any input to the motoneuron, including descending input and afferent input may be greatly modulated. The ease with which synaptic drive to the motoneuron pool results in efferent activity may be subject to considerable change and is termed 'recruitment gain' (Kernell & Hultborn, 1990;Nielsen & Kagamihara, 1993).

3 The primary motor cortex in locomotion

In the previous chapter we saw that several sources may contribute to drive the motoneuron during locomotion, including descending pathways. As previously mentioned, one of the descending pathways is the corticospinal tract with neurons originating from the motor cortex projecting to the spinal cord. There is experimental and clinical evidence to suggest that the motor cortex contributes to drive the motoneuron during locomotion. Such evidence is obtained from studies on cats, but also from different experimental techniques in humans. The current chapter will discuss these studies in brief.

3.1 Evidence from animal studies

Experiments in cats show that during normal unperturbed locomotion 80% of the pyramidal tract neurons are firing in synchrony with the walking cycle (Armstrong & Drew, 1984). Very limited changes were observed in neuronal firing rates when the animals increased speed or walked uphill, despite the fact that the EMG in the hind limb extensors increase with ca. 50% in the latter condition. This is in contrast to a force development task in the hand, in monkeys, where a relation between force and firing frequency could clearly be established (Evarts, 1968; Fetz & Cheney, 1980). There are several explanations for this behaviour. First of all, it may be that the motor cortex only plays a minor role in walking and that the recorded synchrony is only an epiphenomenon. Secondly, it may be that the cortex is involved in walking, but that the adaptation needed to generate increasing muscle activity is of subcortical origin. When the motor cortex or pyramidal tract of a cat is ablated, the animal quickly relearns to walk over a flat surface and only when it is exposed to a more challenging environment like a horizontal ladder the effect of the ablation on walking will be clearly revealed(Trendelenburg, 1911; Liddell & Sherrington, 1924; Armstrong, 1988; Drew *et al.*, 1996).

Although it may be argued that the above-mentioned studies indicate that the motor cortex plays a minor role in overground locomotion, it may also be the case that some deficiences are quickly compensated for by other spinal structures.

3.2 Clinical observations

It has long been recognised that at a lesion of the contralateral sensory motor cortex leads to hemiplegia, and greatly impairs the ability to walk (Knutsson & Richards, 1979; Conrad *et al.*, 1985; Perry *et al.*, 1995; Lamontagne *et al.*, 2007). Only 37% of post-stroke survivors

are able to walk in the first week (Jorgensen *et al.*, 1995) and significant walking disabilities remain in 93% of the patients admitted for rehabilitation (Hill *et al.*, 1997).
These clinical observations are in line with the suggestion that supra-spinal control may play an important role in human locomotion. Interestingly, there are several patients displaying radiological, post mortum histological and clinical evidence of a complete lesion of the CST who still are able to walk (Nathan, 1994; Jang *et al.*, 2005). While the ability to walk may however be largely dependent on compensatory mechanisms, it may also be due to the motor cortex playing a limited role.

3.3 Metabolic activity in the motor cortex during walking

Several methods enable us to study which brain areas are metabolically active during locomotion, including Single Positron Emission Computed Tomography (SPECT ; Fukuyama *et al.*, 1997), Positron Emission Tomography (PET ; Tashiro *et al.*, 2001) and Near Infrared Spectroscopy (NIRS ; Hoshi & Tamura, 1993; Hanakawa *et al.*, 1999; Miyai *et al.*, 2001). A recent study used PET with a radioactively labelled glucose analog to assess the metabolic active brain areas after 10 minutes of walking. They showed prominent activation of the primary motor cortex during real locomotion with PET (la Fougère *et al.*, 2010). Increased metabolic activity in the supplementary motor area and the basal ganglia is seen during both imagined walking (as assessed with BOLD-MRI) and during real walking. This may suggest that mental imagery may activate only a premotor planning mode of locomotion, which involves frontal cortical areas and the basal ganglia, whereas real locomotion represents an executive mode of locomotion driven from primary motor areas. These studies are in line with findings from NIRS tomography, a technique which uses near-infrared light to evaluate the oxygenation of the haemoglobins and which is suitable for examining the outer part of the brain with a high temporal resolution (<0.1 s) (Hoshi & Tamura, 1993). During gait this reveals an increased amount of oxygenated blood in the medial primary sensorimotor cortex and the supplementary motor areas (Hanakawa *et al.*, 1999;Miyai *et al.*, 2001).

3.4 Suppression of the motor cortex during locomotion

The previous section described experiments showing increased metabolic activity in the motor cortex during walking. However, increased metabolic activity does not necessarily signify that the motor cortex contributes to muscle activity. The evidence that the motor cortex contributes to driving the muscle during locomotion was provided using a technique developed by Davey *et al.* (1994), who showed that a magnetic stimulus below

the threshold to elicit a motor evoked potential (MEP) can produce a suppression in the EMG. Several control experiments suggested that this suppression is due to the activation of intracortical inhibitory interneurons which suppress the output from the motor cortex (Davey *et al.*, 1994;Petersen *et al.*, 2001). With this technique it was proven possible to temporarily suppress the EMG activity in SOL and TA during walking, thereby providing evidence that the motor cortex is involved in human walking (Petersen *et al.*, 2001). In study I we used TMS below the threshold to elicit an MEP to investigate whether the motor cortex is also involved in driving SOL during hopping. In Study IV, we were able to reproduce the findings from Petersen *et al.* (2001).

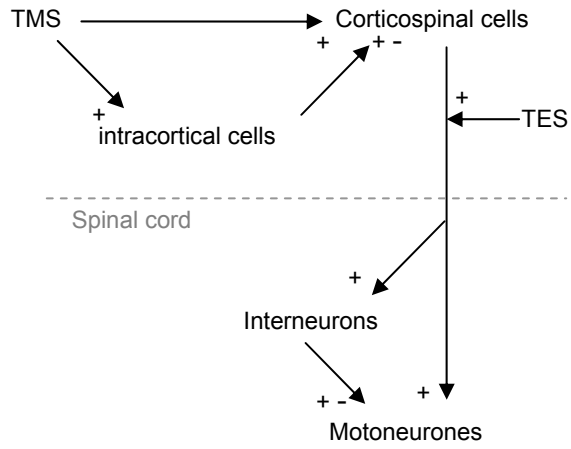

Figure 1, A transcranial magnetic stimulus (TMS) may directly or indirectly excite corticospinal cells. Through intracortical inhibitory interneurons it may also suppress firing of corticospinal cells. Increased excitability of the corticospinal pathway may be attributed to increased excitability anywhere in the pathway including in the intracortical cells, the corticospinal cells, the spinal interneurons or the motoneurons themselves. Transcranial electric stimulation (TES) is thought to excite corticospinal neurons below the axon hillock and is therefore independent of input to the corticospinal cells (Day et al., 1989; Edgley et al., 1990; Burke et al., 1993;Nielsen et al., 1995). Adapted from Petersen et al. (2003).

3.5 Suprathreshold TMS

Capaday *et al.*(1999) used suprathreshold TMS to compare the excitability of the corticospinal pathway between walking and standing with a matched EMG level. They observed greater corticospinal excitability to the soleus during standing compared to

walking and concluded that the corticospinal pathway as a whole is less engaged during the stance phase of walking than during a tonic plantar flexion. However, the observed changes in corticospinal excitability may well be caused by changes in excitability at either spinal or sub-cortical levels as may also be observed in figure 1. Therefore, it is not possible to address the extent to which the sensory motor cortex is involved in walking from this study. Petersen *et al.* (1998) had previously observed that the fast conducting mono-synaptic corticospinal fibres to SOL had a greater excitability during walking than during a tonic contraction. This suggests that the mono-synaptic pathway may play a role during walking. However, the fast mono-synaptic pathway may only constitute a small portion of the corticospinal pathway and it is unknown to what extent this group of neurons contributes to driving the motoneuron. Furthermore, it should be noted that changes in motor cortex excitability do not necessarily reflect an active contribution from corticospinal neurons to the motoneuronal drive during walking.

3.6 Transcortical stretch reflex during locomotion

The evidence presented in this chapter so far supports the idea that the primary motor cortex is involved in unperturbed walking. It is possible that the cortex plays also an important role in reacting to a perturbation during walking. The existence of such a transcortical reflex in the arm was suggested by Hammond (1955), when he observed two bursts of activity in the biceps brachii muscle after a sudden stretch of a human elbow. He speculated that the second burst was mediated by a long trajectory and was possibly mediated by the cortex. The suggestion raised by Philips (1969) that such a reflex was under a more direct influence of the will was supported by experiments from Evarts *et al.* (1974) who showed that the reflex was highly dependent on the on prior instructions.

The first study in the literature on human transcortical stretch reflexes in the lower limb was done in hopping and stepping down. Melvill Jones and Watt (1971) observed a large response around 120 ms after the sudden stretch of the triceps surae muscles after touch-down during hopping. They concluded that this was the first useful muscular reflex response in hopping and therefore labelled it the *functional stretch reflex* (FSR). Based on its latency, the authors suggested that it might be mediated through supra-spinal pathways.

Christensen *et al* (2001) showed a response in TA after a plantar flexion in the mid-swing phase of walking after a plantar flexion perturbation. At interstimulus intervals of 60-120 ms between the stretch and TMS a facilitation of the MEP was seen. By using transcranial electrical stimulation (TES), they showed that this facilitation was of cortical origin and therefore that the late component of the stretch reflex in this situation was likely to have

been mediated by the motor cortex. In the same study they show also that a remarkably large response can be elicited by a plantar flexion in mid-stance. During this phase of the walking cycle, TMS-evoked MEPs are also facilitated by a prior stretch at interstimulus intervals of 60-120 ms. However, the TES-evoked MEPs were also facilitated, suggesting that subcortical pathways are also responsible for the facilitation of the TMS-evoked MEP. It should be noted however that rather high stimulus intensities (33 ± 4% MSO) had to be used to evoke a clear MEP in the inactive TA. Such relatively high intensities may also excite indirect connections to the corticospinal tract and consequently cause a facilitation of the TES-evoked MEP. In study II in this thesis we address the issue using 1Hz repetitive TMS (rTMS), which is thought to temporarily reduce the excitability of the cortex. It is hypothesised that if the large reflex in TA evoked by a plantar flexion in early-stance is indeed mediated by a transcortical pathway, this would also reduce the size of the response.

It was suggested by Sinkjaer *et al.* (1999) that the component of the SOL stretch reflex in walking is also mediated by a transcortical pathway, based on the observation that this reflex is decreased in patients with multiple sclerosis. A decreased nerve conduction velocity in the central nervous system (CNS) in these patients (Caramia *et al.*, 1988; Jones *et al.*, 1991) might cause temporal dispersion between the motor unit action potentials. However, given the large functional differences between TA and SOL, such results cannot necessarily be generalised to SOL. Therefore, we investigated in study III whether such a transcortical reflex also plays a role during walking in SOL.

4 Locomotion as an automated or voluntary activity

In the previous chapter I provided support for the notion that the primary motor cortex plays a role in the control of human locomotion. Traditionally the frontal cortex has been considered the domain of *voluntary* movement (e.g. Porter & Lemon, 1993). Therefore, when the motor cortex is linked to locomotion, the question arises as to whether or not walking may be considered *voluntary*. Semantically and possibly functionally, walking has often been separated from *voluntary* tasks (Morin *et al.*, 1982; Capaday *et al.*, 1990; Lavoie *et al.*, 1997; Schubert *et al.*, 1997; Weerdesteyn *et al.*, 2004). Whether or not walking can be considered *voluntary* is a long-debated question that ties in into a long lasting debate on the meaning of terms like *voluntary*, *automated* and *reflex* (Prochazka *et al.*, 2000). In the current chapter I start off by claiming that the discussion is not purely semantic. First, I will provide arguments for labelling walking as *automated* and will continue with arguments for why walking may be labelled *voluntary*. These arguments may be derived from somewhat subjective experiences in walking, but neuroanatomical arguments are also put forward. At the end of the chapter I will argue that the distinction between walking and *voluntary* tasks may be confusing and should be avoided.

4.1 Hughlings Jackson's continuum: from reflex to voluntary

The neurologist Hughlings Jackson (1884) postulated that the structures of the neural system make up a continuum between *most voluntary* and *most automated*. He described the higher centres as most *voluntary* and most complex whereas the lower centres were described with opposite terms as most *automated* and least complex. An example of the latter structure would be a simple spinal reflex loop. Based on clinical observations and experiments he suggested that the anterior and middle cortex contained the relatively higher centres. The continuum as drawn by Jackson may still be appreciated by today's neuroscientists, and the term *voluntary* is still often linked to higher order structures like the cerebral cortex, whereas *automatic* and *reflex* may be related to lower order neural structures like brainstem and spinal cord. Therefore, the choice to separate walking from a *voluntary* movement may easily lead to the suggestion that higher order centres are less involved and the discussion on whether walking is *voluntary* is not fully semantic.

4.2 Walking as an automated activity

There are several reasons why walking is often considered *automatic*. The suggestion may arise from the subjective experience that we can execute the biomechanical complex task

of bipedal walking without much attention. We can walk large distances over changing terrains while being "absent minded" or while being engaged in a lively conversation. The relative ease with which we perform this rhythmic task may suggest *automaticity*.

This subjective feeling of *automaticity* may be easily linked to the idea that there are structures which are able to act separately from conscious *voluntary* control as is discussed in section 2.1. Indeed if it is agreed upon that *voluntary* control is mediated by supraspinal structures, the ability of the isolated spinal cord to generate stepping movement may give further rise to the suggestion that walking is an *automated* movement. However, it should be noted that while animal experiments give support for an important role of a CPG in locomotion, the role of a spinal CPG in human locomotion is much more uncertain(Duysens et al., 1998).

4.3 Walking as a voluntary task

On the other hand, there are also important arguments to consider walking as a *voluntary* task. One neuro-anatomical argument to term walking as a *voluntary* task is that although the spinal and cerebral preparations discussed above display rhythmic patterns in the absence of patterned stimuli, such activity is rarely observed without electrical, pharmacological or mechanical stimulation. It may thus be speculated that if a spinal pattern generator plays a role in human locomotion, it is likely to be dependent on descending input. This is supported by experiments in which stimulation of the motor cortex in cats or the pyramidal tract may reset the locomotor cycle (Orlovsky, 1972; Armstrong & Drew, 1985; Drew, 1991). This suggests that the motor cortex interacts with the

Box 3: What is more *voluntary*, walking or reaching for popcorn?

We can walk large distances without consciously thinking over each step. This subjective experience of walking has amongst others led to the suggestion that walking is *automated* as opposed to being a pure *voluntary* movement. In contrast, reaching for something is often considered *voluntary*. However, in a recent study, it was shown that when habitual popcorn eaters eat with their dominant hand, they eat the same amount of popcorn, whether stale or fresh (Neal *et al.*, 2011). However, when they eat with their non-dominant hand they would eat less of the stale popcorn. This shows that a reaching movement with their dominant hand was independent of taste, and exemplifies that the distinction *voluntary* versus *automated* is a difficult one. In the perspective of the current study it is difficult to argue why walking is more *automated* than reaching for something.

circuitry that generates locomotion.

In contrast to walking, reaching for something is generally considered to be a *voluntary* task. The study in box 3 nicely exemplifies that reaching out seems rather *automated* in some circumstances and that it is not clear why walking is less *voluntary* than reaching out. It also explicitly makes clear that it is questionable whether our conscious perception is a good measure of which brain areas are involved. However, implicit assumptions about walking and the alleged automaticity of the task may give rise to studies which compare walking with *voluntary* tasks.

4.4 Motor cortex and voluntary muscle activity

Although the motor cortex has been considered of major importance in *voluntary* movement, other structures may also mediate *voluntary* movement. Also *non-voluntary* commands may be mediated by the primary motor cortex. The fact that the relation between motor cortex and *voluntary* activity is not inextricable has been recognised for a long time. Based on a series of experiments conducted in monkeys, where the pyramidal tract was lesioned, it was noticed by Tower (1940) that: *"although traditionally the pyramidal system has been considered the voluntary motor pathway, this is too sweeping. An impressive capacity for voluntary movement survives pyramid section"*. Indeed, monkeys with lesions to the primary motor cortex or pyramidal tract may only show deficits in small and differentiated finger movements (Tower, 1940; Lawrence & Kuypers, 1968).

While the primary motor cortex is not the only source of *voluntary* drive, it is also not true that output from the motor cortex is always *voluntary*. In section 3.6 it was discussed how the transcortical stretch reflex may play a role in walking and maybe in hopping. The transcortical stretch reflex has strong reflex characteristics because the response follows shortly after specific sensory input. On the other hand, because a transcortical reflex has been shown to be highly dependent on instruction in the hand muscles, such reflexes may be considered to be under some *voluntary* control (Evarts & Tanji, 1974). Therefore, the transcortical stretch *reflex* can be considered somewhere in the middle on the continuum between *most voluntary* and *most reflex* (Jackson, 1884). The existence of this reflex during walking was suggested by Sinkjaer *et al.* and later shown by Christensen *et al.* (2001) and it's role during walking is further studied in study II and III.

4.5 Concluding remarks

The main danger in using the terms *voluntary*, *automated* or *reflex* in relation to any movement, but particularly in relation to walking is that there may be implicit assumptions about the neuro-anatomic control of the task. The best way of avoiding this problem is to abandon the use of these terms especially when it comes to walking.

Contribution of afferent feedback and descending drive to human hopping

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Abraham T Zuur [1,2,3]
Jeer Lundbye-Jensen [1,2]
Christian Leukel [4,5]
Wolfgang Taube [4]
Michael J Grey [1,2]
Albert Gollhofer [4]
Jens Bo Nielsen [1,2]
Markus Gruber [4,6]

1 *Department of Exercise and Sport Sciences, Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark*

2 *Department of Neuroscience and Pharmacology, Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark*

3 *Center for Sensory-Motor Interaction, Aalborg University, Fredrik Bajers Vej 7-D3, DK-9220 Aalborg, Denmark*

4 *Department of Sport Science, University of Freiburg, Schwarzwaldstr. 175, 79117, Freiburg, Germany*

5 *Spinal Cord Injury Centre, University Hospital Balgrist, Zürich, Switzerland*

6 *Department of Training and Movement Science, University of Potsdam, Am Neuen Palais 10, 14469 Potsdam, Germany*

Tibialis anterior stretch reflex in early stance is suppressed by repetitive transcranial magnetic stimulation

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Abraham T Zuur,1,2,3
Mark S Christensen,2,3,4
Thomas Sinkjær,1
Michael J Grey,1,2,3
Jens Bo Nielsen2,3

1 *Center for Sensory-Motor Interaction, Aalborg University, Fredrik Bajers Vej 7-D3, DK-9220 Aalborg, Denmark*

2 *Department of Exercise and Sport Sciences, Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark*

3 *Department of Neuroscience and Pharmacology, Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark*

4 *Danish Research Centre for Magnetic Resonance, Hvidovre University Hospital, Ketteg°ard All´e 30, DK-2650, Hvidovre, Copenhagen, Denmark*

Stretching the active muscle facilitates cortical and subcortical pathways to the antagonist during walking

Abraham T. Zuur[1,2,3]
Thomas Sinkjær[1,4]
Jens Bo Nielsen[2,3]
Michael J. Grey[1,2,3,5]

1 *Center for Sensory-Motor Interaction, Aalborg University, Fredrik Bajers Vej 7-D3, DK-9220 Aalborg, Denmark*

2 *Department of Exercise and Sport Sciences, Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark*

3 *Department of Neuroscience and Pharmacology, Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark*

4 *Danish National Research Foundation, Copenhagen, Denmark*

5 *School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom*

Intracortical inhibition during human walking and standing

Abraham T. Zuur[1,2,3]
Monica A. Perez[1,2,5]
Thomas Sinkjær[3,4]
Jens Bo Nielsen[1,2]
Michael J. Grey[1,2,3,6]

1 *Department of Exercise and Sport Sciences, University of Copenhagen, Copenhagen N, Denmark*
2 *Department of Neuroscience and pharmacology, University of Copenhagen, Copenhagen N, Denmark*
3 *Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark*
4 *Danish National Research Foundation, Copenhagen, Denmark*
5 *Department of Physical Medicine and Rehabilitation, Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA USA*
6 *School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom*

Intracortical inhibition during force modulation

Abraham T. Zuur[1,2,3]
Monica A. Perez[1,2,5]
Thomas Sinkjær[3,4]
Jens Bo Nielsen[1,2]
Michael J. Grey[1,2,3,6]

1 *Department of Exercise and Sport Sciences, University of Copenhagen, Copenhagen N, Denmark*

2 *Department of Neuroscience and pharmacology, University of Copenhagen, Copenhagen N, Denmark*

3 *Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark*

4 *Danish National Research Foundation, Copenhagen, Denmark*

5 *Department of Physical Medicine and Rehabilitation, Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA USA*

6 *School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom*

5 Discussion of the studies

In this current chapter the main message of the thesis will be presented and the relation between it and the other papers in the thesis will be discussed.

5.1 Study I: Contribution of afferent feedback and descending drive to human hopping

Reflexes work in concert with higher order structures like the primary motor cortex to produce a repetitive movement such as hopping.

At a first glance study I does not seem to fit in with the rest of the studies. While all the other studies are about walking, this one is about hopping. It is included because the finding that descending drive and spinal reflexes contribute to a repetitive task shows similarities with walking. Also in walking it is shown that both the motor cortex (Petersen *et al.*, 2001) as well as pathways mediating afferent feedback (Sinkjaer *et al.*, 2000) contribute to the task. Nielsen & Sinkjaer (2002) stress that it is important to make the distinction between the afferent drive to the motoneuron during normal unperturbed walking and the feedback generated during an unexpected perturbation (Nielsen & Sinkjaer, 2002). Interestingly, it is hard to apply the distinction between reflex and afferent drive to the *moving platform protocol* as part of the movement. The synchronised afferent information when generated as a result of the touchdown, produces the first peak in the EMG while hopping. Although it is technically not an error signal, it shows large similarities with the error signal as generated by the error signal, in turn generated by a perturbation, during sitting (Berardelli *et al.*, 1982) or walking (Sinkjaer *et al.*, 1996). While this reflex is externally produced during sitting and walking, in hopping the stretch is part of the ongoing movement. The distinction between the afferent drive to the motoneuron during unperturbed walking, and the feedback generated during an unexpected perturbation, seems not to be applicable to hopping.

5.2 Study II: Tibialis anterior stretch reflex in early stance is suppressed by repetitive transcranial magnetic stimulation

In study I it was shown that descending drive from the motor cortex can work in concert with spinal reflexes. In study II we investigated whether the large reflex seen during the mid-stance phase in walking is mediated by the cortex. Such pathways in walking had been suggested before in the swing phase of walking (Christensen *et al.*, 2001) and underlines the integrative nature of the neural system.

Study II shows that the remarkably large stretch reflex evoked in the TA by plantar flexion perturbation in the an early stance phase is at least partly mediated by a transcortical pathway, underlining the notion that the motor cortex interacts with proprioceptive feedback in order to cope with the complex demands of walking.

In section 5.3 we integrate this finding with study III.

5.3 Study III: Stretch induced afferent input affects cortical and subcortical pathways to the soleus muscle in different phases of the step cycle

In study II we show that afferent information from the ankle dorsiflexor muscles projects to the motor cortex when a sudden plantar flexion is delivered in mid-stance. In study III we examine whether afferent input from TA also projects to the cortical area that controls its antagonist SOL. This is examined in the mid-swing phase of walking. We also examined whether information from SOL elicited in the mid-stance phase relayed to the motor cortex.

Study III shows that afferent information from SOL elicited during stance is relayed to sub-cortical structures controlling SOL, while afferent input from TA-elicited during swing phase is relayed to the motor cortex.

In study II and study III the influence of afferent input on the excitability of the motor cortex is studied. In the discussion of study III we speculate on whether the relaying of afferent firing to the motor cortex is dependent on the phase in the step cycle or on specific muscle afferents. To further elaborate on this question we summarise the (preliminary) results of previous and ongoing studies in table I.

	Afferents → target muscle	Gait cycle	Results	Origin of facilitation	Source
a.	R.Fem → L. SOL	at heel strike	TMS facilitated TES facilitated H-reflex not increased	Subcortical	Stecina, preliminary results unpublished
b.	sTA → TA	early stance	TMS facilitated TES facilitated	Subcortical?	Christensen *et al*, 2001
c.	sTA → TA	early stance	1 Hz rTMS decreases reflex	Cortical	Zuur *et al*, 2009
d.	sSOL → SOL	stance	TMS facilitated TES facilitated	Subcortical	Study III
e.	sTA → TA	swing	TMS facilitated TES not facilitated	Cortical	Christensen *et al*, 2001
f.	sTA → SOL	swing	TMS facilitated TES not facilitated	Cortical	Study III

Table 1, Summary of the results of the origin of afferent induced facilitation of the TMS-evoked MEP. With the exception of the first study, all studies are performed on the left leg. R.Fem – electrical stimulation of the right femoral nerve. L. SOL – left soleus muscle, sTA – stretch of the tibialis anterior muscle (plantar flexion perturbation), sSOL – stretch of the soleus muscle (dorsiflexion perturbation). Grey areas indicate that the reflex is thought to be mediated by the cortex.

The areas shaded in grey in table 1 indicate a reflex pathway which is most likely to be mediated by the cortex. It may be noted that the studies in which TA afferents are stimulated show a transcortical connections. These afferents from TA may project to cortical areas controlling SOL (row f.) as well as areas controlling TA (row c. and e.). In contrast, afferents from SOL (row d.) or from the contralateral femoral nerve (row a.) do not seem to influence the corticospinal excitability so strongly. We may speculate that afferents from TA have more influence at a cortical level than afferents from SOL. This would be in line with the suggestion that the TA has stronger corticospinal connections than SOL (Jankowska *et al.*, 1975; Asanuma *et al.*, 1979; Brouwer & Ashby, 1992; Bawa *et al.*, 2002)

Alternatively, it may also be noted that the studies in swing both show a cortical origin for afferent induced facilitation of the MEP (row e. and f.). The only study in stance showing cortical facilitation is study II, where we show that the large reflex evoked by a plantar flexion perturbation in early stance is mediated by the motor cortex. This may be

explained by the fact that in this experiment the early stance phase is studied. In the early stance phase, weight from one leg is transferred to the other and it therefore a critical part of the step cycle. If a perturbation occurs during this time, a corrective response may help in maintaining balance and also here it may be beneficial to have cortical control. This explanation is not supported by preliminary results from a study in which the contralateral femoral nerve is stimulated at heel strike. In these experiments both the TMS-evoked MEP as well as the TES-evoked MEP were facilitated after stimulating the contralateral femoral nerve, suggesting a subcortical origin of the facilitation. However, unlike the other studies, this study is testing stimuli which test facilitation to a muscle at the contralateral side of the body.

To summarise, it is still unclear why some studies show subcortical mediated facilitation and others show a cortically mediated facilitation. Although methodological issues may contribute to this, it may also be that the afferents from different muscles project with different strength to the cortex. Alternatively it may be that the facilitation is dependent on a particular phase of the step cycle. Future research may point to which of these is the case.

5.4 Study IV: Intracortical inhibition during human walking and standing

In study II and III we showed that afferents from the leg project to the motor cortex and thereby influence the excitability of the corticospinal neurons. In study IV we examine the influence of intracortical inhibitory interneurons.

Study IV shows that during both walking and standing intracortical inhibition is decreased, possibly to let corticospinal neurons fire. A decreased ability to suppress muscle activity during walking by exciting intracortical inhibitory interneurons may be explained by a smaller cortical contribution during walking or by a decreased ability to suppress cortical- or spinal neurons during walking.

In study IV we see that the ability to suppress muscle activity with a subthreshold magnetic stimulus is less during standing than during walking. Due to the often highly non-linear behaviour of the CNS, this finding cannot be explained unequivocally. One of the difficulties in explaining the finding is that we compare walking with standing, and they may have many differences in corticospinal and motoneuronal firing. Also, while during standing, only small corrections in muscle length are made; the mid-stance phase of walking is a dynamic contraction. To be able to compare a static and a dynamic contraction, study V was performed.

The differences between the behaviour of the TMS_{ES} and SICI when walking and standing give rise to several hypotheses, all of which are discussed in the study, and a number of explanations are given for the outcome, providing a good basis for further research projects. Nonetheless, the study lacks some precision in that it proves difficult to derive the amount of corticospinal drive from the methods used with any reasonable certainty. In the case of this particular piece of research carried out at a fairly basic scientific level, pilot experiments were conducted on unexplained phenomena thought worthy of investigation. The approach led to some interesting discoveries, though had open ended results, and there is a good opportunity in the future for these initial findings to be reformulated into a new well-defined research question.

5.5 Study V: Intracortical inhibition during force modulation

Intracortical inhibition is decreased during force increment, a period with presumed increased corticospinal output. However, no change in the ability to suppress muscle activity by exciting intracortical interneurons is seen during this time. Although a relation between the ability to suppress the corticospinal output and the amount of corticospinal output is suggested, the measured effects cannot be explained unambiguously.

6 Summary, final conclusions and further research

6.1 Summary of the studies

The core of the thesis comprises a set of five original research papers on how the primary motor cortex contributes to walking and hopping, and how afferent feedback to the motor cortex, descending drive and spinal reflex loops, all contribute to a functional rhythmic movement. How spinal reflex loops and descending drive work in concert in producing a rhythmic movement is exemplified in **study I**. Just as in walking, hopping is a task in which reflexes are suggested to play an important role, and it is unknown whether the motor cortex further contributes to such a reflex. We showed that reflexes indeed play an important role during the first peak of muscle activity in the soleus muscle (SOL) observed after ground contact during hopping. Interestingly, the motor cortex also contributes to driving the motoneurons during this time, showing that afferent feedback and descending drive work in concert. In the subsequent three studies we examined the influence of the motor cortex in walking. In **study II** and **study III** we studied afferent input during walking and the role of the motor cortex in processing it. In **study II** we answered the question whether the large long-latency stretch reflex seen in the tibialis anterior after a sudden plant flexion in the mid-stance phase of walking is mediated by the primary motor cortex. We used repetitive TMS to suppress the leg area of the motor cortex and thereby reduced the excitability of the motor cortex. The long-latency stretch reflex reduced concomitantly and, supported by further control experiments, we concluded that the reflex is at least partly mediated by a transcortical reflex loop. In study II and in previous studies it was shown that afferent information may be fed back to the homonymous muscle, but recent reports in sitting suggested that afferent input may also affect cortical areas controlling antagonist muscles. In **study III** we showed that a sudden plantar flexion perturbation in mid-swing during walking, thus stretching antagonist muscles, increased the cortical excitability of the area projecting to SOL. Interestingly, when a dorsiflexion perturbation in mid-stance is given, thus stretching agonist muscles, this feedback to SOL is mediated through subcortical pathways. **Study IV** is built on the notion that the output from corticospinal neurons is under the influence from both inhibitory and excitatory intracortical interneurons. Previous studies have suggested that a decreased excitability of intracortical inhibitory interneurons may reflect the functional necessity to decrease intracortical inhibition to let corticospinal neurons fire. We showed that while it seemed that the excitability of the intracortical inhibitory interneurons did not change during walking compared to standing, it was more difficult to suppress ongoing muscle activity in SOL during walking. This may be explained by a smaller corticospinal

drive during walking. Alternatively, it may be that it is less easy to inhibit cortical or motoneuronal output during walking, since SOL is in a dynamic contraction during stance. To further evaluate the effect of a dynamic contraction compared to a static contraction, we measured the effect of exciting intracortical inhibitory interneurons during a ramp-and-hold force trajectory in **study V**. Based on previous studies, it was suggested that there is more corticospinal output during the rising section of the ramp. The measured changes in intracortical inhibition could be related to this finding. However, based on these results it may not be possible to derive changes in cortical output from changes in the effect of intracortical inhibition.

6.2 Conclusions of the thesis

The findings in this thesis underline the integration of the motor cortex in the rhythmic tasks of like walking and hopping by showing that:

- Spinal reflex loops and descending drive work in concert to produce a rhythmic movement like hopping.
- Stretch reflex pathways from the ankle dorsiflexors in mid-stance are mediated by the motor cortex further showing the integrative nature of descending drive and reflex pathways.
- Input from antagonist muscles during mid-swing, project to the cortical area controlling the soleus muscle, thus showing how afferent information from the antagonist is integrated at a cortical level in a way which is different from its use at a spinal level.
- Cortical output contributes to driving the motoneuron during both standing and walking. The effect of exciting intracortical inhibitory pathways during walking produces less suppression than during standing.
- The terms *voluntary*, *automated* or *reflex* in relation walking should be avoided because they often implicitly refer to the neuroanatomic area where the movement is controlled.

Box 4: Nothing stops us from walking

The integrative control of human locomotion outlined in the final conclusions probably contributes to our ability to adapt to different fields and withstand perturbations. During my PhD I have been involved in many walking experiments. To get further insight into the control of walking, neurophysiologists induce perturbation using a wide variety of methods. This includes perturbation with a portable stretch device (study II and III), using transcranial magnetic stimulation to generate additional muscle activity in the leg muscles (study II, III and IV), transiently reducing the activity in the leg muscle by taking away drive from the motor cortex (study I and IV), and deriving it from muscle afferents (Sinkjaer *et al.*, 2000;af Klint *et al.*, 2008). The neuromechanical system generating the walking movement may be further challenged when a tourniquet is placed just above the knee to temporarily stop the blood flow thereby blocking nerve conduction in the large afferent nerves (Grey *et al.*, 2001), or by pharmacological interventions which change the way our nerves transmit signals (Mazzaro *et al.*, 2005).

We often combine these techniques. Despite this, an intervention rarely changes our walking pattern drastically or perturbs us so much that we cannot continue walking. Just watching and working in the laboratory made me realise the enormous neurophysiological and biomechanical redundancies in healthy people, which keep us walking whatever happens. The integration between motor cortex and subcortical structures may well contribute to this redundancy.

6.3 Future perspectives

The studies in the thesis contribute to further understanding of the neural control of human walking and in turn open up a wide spectrum of unknowns, which will hopefully lead to further research.

6.3.1 Afferent feedback relaying to the motor cortex: phase or muscle specific

In study III we found that afferent information from SOL elicited during standing is relayed to sub-cortical structures controlling SOL, while afferent input from TA-elicited during swing phase is relayed to the motor cortex. In the discussion of this study and in the section 5.3, we speculate on whether this difference is more muscle or phase specific.

The question is important also in rehabilitation. The question is whether the focus should be directed to certain muscles, or is it more important to focus at a certain phase of the step cycle?

6.3.2 Role of the motor cortex in learning and attention in walking?

In the current thesis we have further established a role for the primary motor cortex in driving the motor neuron and in mediating afferent feedback. It can be hypothesised that the role of the motor cortex in locomotion may be much broader and may also play a role in learning how to handle new demands, or may be more involved if the task requires increasing attention. Indeed, a recent study from Barthélemy *et al* . (2012) suggests that the corticospinal tract contributes in a task-specific manner to gait adaptations.

Indeed, very preliminary results support the suggestion that the primary motor cortex is involved in attention. In the experiment subjects first had the task of walking unperturbed. In a second task they were instructed to direct attention to their legs in order to counteract an ankle perturbation in mid-swing. This perturbation was either a dorsiflexion or a plantar flexion. In both conditions the TMS_{ES} was measured in the unperturbed steps. The TMS_{ES} was measured in two subjects and showed an increase in the attention task. The experiment needs to be repeated in more subjects and control experiments need to be carried out to test whether the increase in TMS_{ES} is due to attention or to the perturbations which may occur.

The question of whether the motor cortex is involved in learning and attention during walking is also relevant in the context of rehabilitation. Based on the ability of the mammalian spinal cord to relearn weight bearing after a complete spinal cord dissection, some authors stress the relative importance of the spinal cord in locomotion after a spinal cord injury (Harkema, 2001; Dietz, 2006). However, the chapters of the current thesis as well as the original articles provide further support for the idea that the motor cortex plays a role in human walking. This gives further support to the idea that the effects of rehabilitation are partly dependent on the ability to use the remaining descending pathways to exhibit cortical or at least supraspinal control.

7 References

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About the author

Bram Zuur was born in Damwâld, the Netherlands, in 1979. He started his school education at 'de Fontein' in Damwâld from 1983 to 1991. He went to the Dockinga College in Dokkum where he received in 1997 his certificate for 'preporatory scientific education' (VWO). He completed the first year (propedeuse) of Applied Science at the University of Twente and continued subsequently to Electronic Engineering. January 2003 he completed his Master in Electronic Engineering. During the master he specialised in Biomedical Engineering and the title of his Master thesis was "Characterising Parkinson's disease by measuring the response of the forearm to perturbations". The work as presented in the current thesis was carried out at Aalborg University and Copenhagen under supervision of Jens Bo Nielsen, Michael James Grey and Thomas Sinkjær. After 2 years of research he took a break from his PhD and started studying medicine. In 2007 he continued with the PhD. The Master in Medicine was completed in 2011. Today Bram Zuur is working as a resident in Internal Medicine at the Medisch Spectrum Twente in Enschede.