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BY
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On rate enhancement during the human voluntary rhythmic movement of finger tapping

Ph.D. Thesis

By

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AALBORG UNIVERSITY
DENMARK

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ENGLISH SUMMARY

Voluntary rhythmic movements are fundamental during everyday human life. Examples of such movements include walking and other cyclic tasks, such as finger tapping. It has been shown that motor function of voluntary rhythmic movement can be altered through e.g. priming, which can be described as a change in behaviour generated by a preceding stimulus. However, many details of the control and regulation of voluntary rhythmic movements involved in priming remain largely undisclosed. Thus, an improved understanding of the nervous system's function in general but also for potential medical use and development of e.g. exoskeletons or robotic assistance is useful.

A behavioural priming phenomenon, termed 'repeated bout rate enhancement', has been revealed previously. The phenomenon comprises that the freely chosen tapping rate during voluntary index finger tapping was increased following submaximal muscle activation, in form of finger tapping. It has previously been proposed that finger tapping could be a central pattern generator-mediated rhythmic movement and further that the observed rate enhancement could be the result of a net excitation of the supraspinal centres, the spinal central pattern generator, or a combination of both. The overall aim of this thesis was to increase our understanding of voluntary stereotyped rhythmic movements. More specifically, the main purpose was to investigate and further elucidate the phenomenon of repeated bout rate enhancement during the task of finger tapping. For this purpose, three studies were performed.

In study I, various forms of finger tapping were investigated. It was shown that repeated bout rate enhancement could be elicited following passive tapping, which does not require descending drive. In study II, various durations of the first tapping bout were applied. Here it was revealed that rate enhancement was elicited following tapping durations ranging from 20 s to 180 s in the first bout. The results showed that there was no dose-response relationship between the duration of priming and the magnitude of rate enhancement. In study III, linear and non-linear metrics applied to kinetic and kinematic time series were calculated in an attempt to investigate possible differences in motor variability between responders and non-responders (i.e., individuals showing and not showing repeated bout rate enhancement, respectively). Of note is that a responder was defined as an individual who showed a minimum increase of 3% of the freely chosen tapping rate from the first to the second tapping bout. Here it was revealed that responders and non-responders demonstrated different characteristics of motor variability, primarily related to the complexity in the structure of motor variability.

The present findings are interpreted to suggest that rate enhancement during finger tapping could be the result of an increased excitability of the nervous system, which to a certain extent could be caused by sensory feedback. Furthermore, that a duration of as little as 20 s of priming seems to be sufficient to elicit rate enhancement. Finally, that individuals who show repeated bout rate enhancement could exhibit a greater adaptability in the dynamics of motor control compared with individuals who do not show repeated bout rate enhancement

DANSK RESUMÉ

Frivillige rytmiske bevægelser er grundlæggende i menneskers hverdag. Eksempler på sådanne bevægelser inkluderer gang og andre cykliske opgaver, såsom finger tapping. Det er påvist, at den motoriske funktion af frivillige rytmiske bevægelser kan ændres gennem f.eks. 'priming', der kan beskrives som en ændring i adfærd genereret af en forudgående stimulus. Dog er mange detaljer om kontrol og regulering af frivillige rytmiske bevægelser involveret i f.eks. priming fortsat uafklaret. En forbedret forståelse af nervesystemets funktion generelt, men også til potentiel medicinsk brug og udvikling af f.eks. eksoskeletter eller robot-assistance kan være nyttig.

Et fænomen som har med motorisk adfærd at gøre, kaldet 'repeated bout rate enhancement', er tidligere blevet påvist. Fænomenet omfatter, at den frit valgte tappehastighed under frivillig pegefinger tapping var øget efter submaximal muskelaktivering, i form af finger tapping. Det er tidligere blevet foreslået, at finger tapping kan være en 'central pattern generator'-medieret rytmisk bevægelse og endvidere, at den observerede hastighedsforøgelse kan være resultatet af en netto-excitation af supraspinale centre, den spinale central pattern generator eller en kombination af begge. Det overordnede formål med denne PhD afhandling var at øge vores forståelse af frivillige stereotype rytmiske bevægelser. Mere specifikt var hovedformålet at undersøge og yderligere belyse fænomenet repeated bout rate enhancement under udførelsen af finger tapping. Til dette formål blev der udført tre studier.

I studie I blev forskellige former for finger tapping undersøgt. Det blev vist, at repeated bout rate enhancement kunne fremkaldes efter passiv tapping, hvilket ikke kræver descenderende drive. I studie II blev forskellige varigheder af den første tappe-bout anvendt. Her blev det vist, at rate enhancement blev fremkaldt efter tappe bouts med varigheder fra 20 s til 180 s i den første bout. Resultaterne viste, at der ikke var noget dosis-respons-forhold mellem varigheden af priming og omfanget af rate enhancement. I studie III blev lineære og ikke-lineære mål beregnet på kinetiske og kinematiske tidsserier, i et forsøg på at undersøge mulige forskelle i motorisk variabilitet mellem respondenter og ikke-respondenter (dvs. individer der henholdsvis viser og ikke viser repeated bout rate enhancement). Det skal bemærkes, at en responder blev defineret som et individ, der viste en minimumsforøgelse på 3% af den frit valgte tappehastighed fra den første til den anden tappe bout. Her blev det vist, at respondenter og ikke-respondenter demonstrerede forskellige karakteristika af motorisk variabilitet, primært relateret til kompleksiteten i strukturen af motorisk variabilitet.

De indeværende fund kan tolkes i retning af, at rate enhancement under finger tapping kan være et resultat af en forøget excitabilitet i nervesystemet, som til en vis grad kan være forårsaget af sensorisk feedback. Endvidere ser det ud til, at en varighed på så lidt som 20 sekunders priming synes at være tilstrækkelig til at fremkalde rate enhancement. Slutteligt, at individer der viser repeated bout rate enhancement, udviser en større tilpasningsevne i dynamikken af motorisk kontrol sammenlignet med individer, der ikke viser repeated bout rate enhancement.

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First and foremost, I want to thank my principal supervisor, Associate Professor Ernst Albin Hansen, for his supervision, the detailed feedback and persistent perfectionism. I want to express my gratitude to my co-supervisor, Professor Michael Voigt, for his priceless help in the laboratory and development of analysis scripts, and our many scientific discussions at his office. Also, I want to thank Professor Pascal Madeleine for his high expertise towards the development of experimental designs and valuable feedback in all of the studies. I have gained a great amount of knowledge and experience from working with you all, and for this, I am truly grateful.

Completion of the current thesis was greatly aided by external funding. Therefore, I want to acknowledge the generous economic support from The Ministry of Culture Committee on Sports Research in Denmark. I also appreciate and thank the great number of participants who volunteered in the experiments of the entire Ph.D. study.

Finally, I would like to acknowledge the support I have received from family and friends. Especially, I want to thank my wife Pia, for her endless encouragement, love and belief in me. The completion of the Ph.D. study, would not have been possible without you

PREFACE

The present studies were carried out in the period 2016 to 2019 at the Sport Sciences group, Department of Health Science and Technology, Aalborg University, Denmark. The current Ph.D. stipend was funded by Aalborg University.

The thesis is based on the following three articles. In the text these are referred to as study I, study II, and study III (full-length articles in Appendix).

Study I Emanuelsen, A., Voigt, M., Madeleine, P., Kjær, P., Dam, S., Koefoed, N., Hansen, E. A. Repeated bout rate enhancement is elicited by various forms of finger tapping, Frontiers in Neuroscience (2018), 12:526.

Study II Emanuelsen, A., Voigt, M., Madeleine, P., Hansen, E. A. Effect of tapping bout duration during active and passive finger tapping on elicitation of repeated bout rate enhancement, submitted.

Study III Emanuelsen, A., Madeleine, P., Voigt, M., Hansen, E. A. Motor variability in elicited repeated bout rate enhancement is associated with higher sample entropy, Human Movement Science (2019), 68:102520.

Contents

LIST OF ABBREVIATIONS

ANOVA:	Analysis of variance
CPG:	Central pattern generator
CV:	Coefficient of variation
EDC:	Extensor digitorum communis
EEG:	Electroencephalography
EOG:	Electrooculogram
FDS:	Flexor digitorum superficialis
$ICC_{(3,1)}$:	Intraclass correlation coefficient
LED:	Light emitting-diode
MCtx:	Motor cortex
MLR:	Mesencephalic locomotor region
MVC:	Maximal voluntary contraction
MVE:	Maximal voluntary electromyographic
RBRE:	Repeated bout rate enhancement
RMS:	Root mean square
SaEn:	Sample entropy
SD:	Standard deviation
sEMG:	Surface electromyography
SEP:	Sensory evoked potential

1 INTRODUCTION

This section presents a background and scope of the present project. The overall aims of the thesis are also presented.

1.1 Motor control and rhythmic movements

In everyday behaviour, a well-developed motor control is fundamental for the ability to perform consistent and precise movements (Swinnen 2012). It has been proposed that two types of movement constitutes primitives for more complex behaviour: rhythmic and discrete movements (Hogan & Sternad 2007). In extension hereof, it has been argued that rhythmic movements, such as breathing, walking, or chewing are old motor behaviours found in many species, whereas discrete movement, such as reaching and grasping, has been developed through years of evolution in younger species, particularly primates (Schaal et al. 2004). Furthermore, distinctly different neural control mechanisms of rhythmic and discrete movements has been shown, with several higher cortical planning areas involved in discrete movement compared with rhythmic movement (Schaal et al. 2004). The focus of the present project revolves around the neuromuscular control of rhythmic movements.

For humans, rhythmic movement is a fundamental part of everyday life, enabling us to interact with our surrounding environment without the need of assistance. Thus, patients with impaired neural or motor function are often taking part in rehabilitation programmes to maintain or improve motor control (Jacobs & Nash 2004, Schwartz et al. 2011). Therefore, understanding the neuronal mechanisms underlying the neuromuscular control of rhythmic movements has the potential to provide a better understanding of nervous system function in general but also for medical use and development of e.g. robotic assistance or exoskeletons.

Voluntary rhythmic movements include walking, running and pedalling. Commonly for the activities, they have been used as exercise models for human rhythmic movement studies (Zehr & Duysens 2004, Sakamoto et al. 2007, Zehr et al. 2007, Hansen & Ohnstad 2008, Hundza & Zehr 2009, Stang et al. 2016). Moreover, finger tapping is a stereotyped voluntary rhythmic movement, which has been used as an exercise model in both asymptomatic (Sternad et al. 2000, Aoki et al. 2005, Wu et al. 2008, Sardroodian et al. 2016) and patients with neural disease, such as e.g. Parkinson's disease (Yokoe et al. 2008, Keitel et al. 2013, Teo et al. 2013, Adams 2017). Voluntary rhythmic movements, such as for example finger tapping, can be performed consciously (i.e. paced) or automated (i.e. freely chosen). Freely chosen finger tapping can be classified as a stereotyped rhythmic movement, which is thought to be highly automated and requires less brain-activity

(Kawashima et al. 1999) compared with paced finger tapping. In extension, Kawashima et al. (1999) reported that freely chosen tapping showed less supraspinal activity compared to various frequencies of paced tapping, which was attributed to a more automatic and easier generation of motor performance. This is in line with the understanding that automation does not require conscious input and is mainly regulated by spinal contribution (Zehr et al. 2004, Power et al. 2018), whereas conscious input is mainly regulated by cortical areas (Schaal et al. 2004, Hogan & Sternad 2007). Thus, the focus of the present project will primarily relate to voluntary stereotyped rhythmic movement using finger tapping as an exercise model.

1.2 Neuromuscular control of voluntary stereotyped rhythmic movements

It has been suggested that the freely chosen tapping rate during index finger tapping is controlled by a tripartite system, consisting of spinal central pattern generators (CPG's) in an interrelationship with supraspinal descending drive and sensory feedback (Hansen & Ohnstad 2008, Shima et al. 2011), see **Figure 1**.

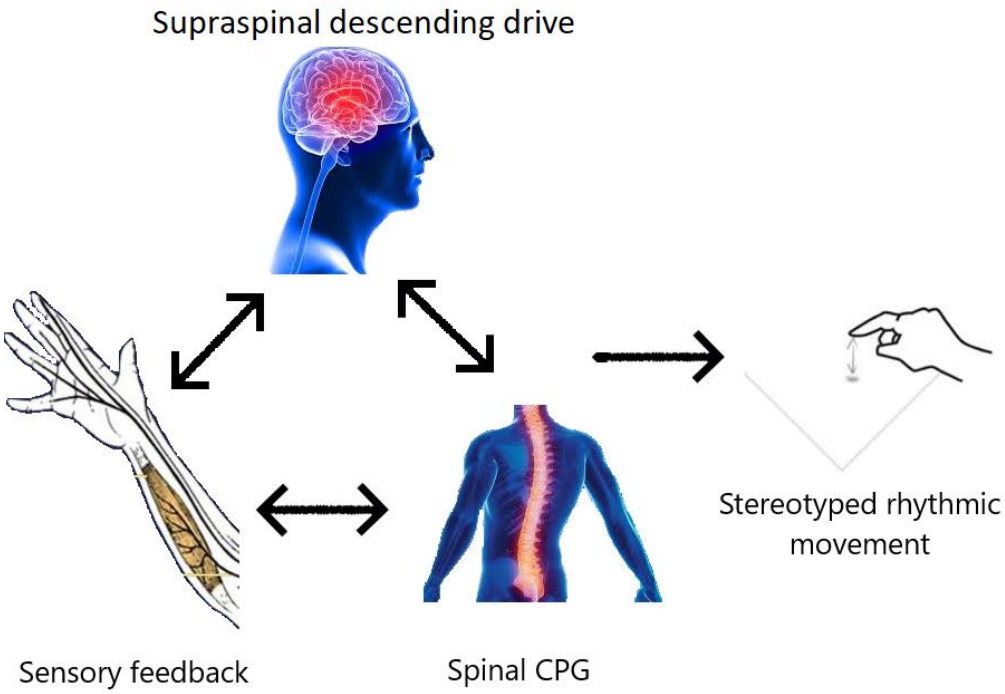

Figure 1. Illustration of the tripartite system for the regulation of human stereotyped rhythmic movement. Based on previous work, including Zehr & Duysens (2004) and Zehr (2005).

However, the tripartite system include components that can interact with each other through a complex variety of possible interactions. A conceptualized model for the possible organization of the neural control of rhythmic movement is presented in **Figure 2**.

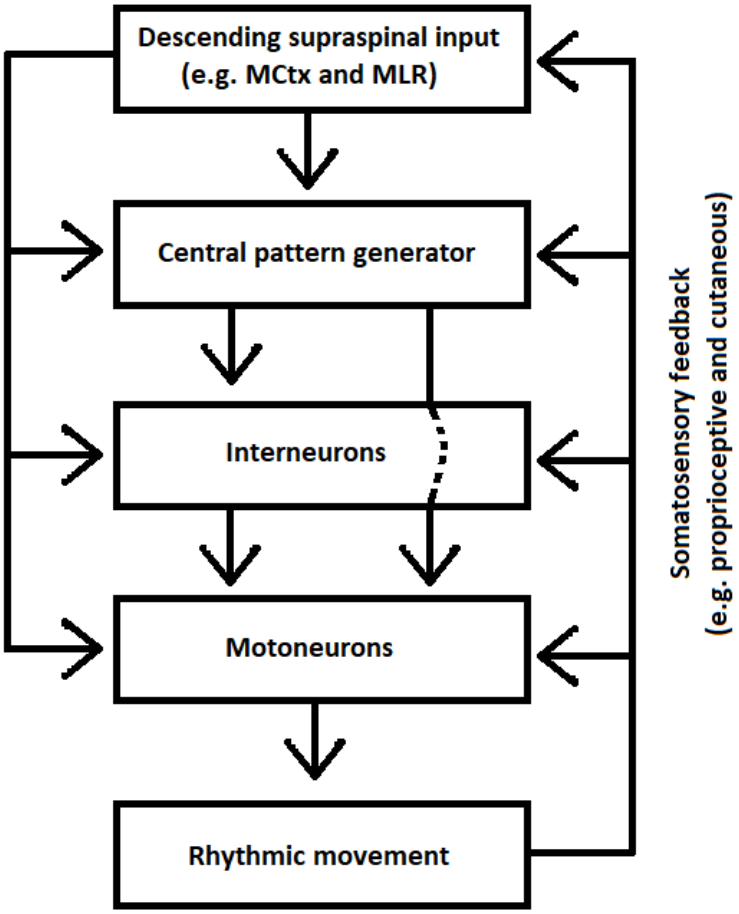

Figure 2. A conceptual model of the possible organization of the neural control regulating rhythmic movement in humans. Based on previous work, including Burke et al. (2001), Zehr et al. (2004) and Zehr (2005). MCtx = motor cortex, MLR = mesencephalic locomotor region

The three main components of the tripartite system and their possible underlying interactions will be presented in more detail in the following section.

1.2.1 Supraspinal descending input from cortical areas

The supraspinal connectivity of rhythmic movement has mostly been described for locomotion in vertebrates, and much of our present knowledge on the supraspinal organization and control of rhythmic movement stems from work performed on animal preparations (Shik et al. 1969, Armstrong 1988). Thus, it must be noted that a similar control of locomotion and finger tapping cannot be

concluded, just like the translation of control between animals and humans. However, an overall similar control of rhythmic movements can be assumed to an extent (Zehr et al. 2004, Frigon 2017). Thus, the following section is regarded as a brief presentation of the general understanding of the supraspinal neuronal control of rhythmic movements and is based on a recent review by Kiehn (2016). On **Figure 3** it can be seen that the selection and initiation of rhythmic motor behaviour involves several regions of the brain and brainstem. The basal ganglia (BG) is responsible for the selection of behaviour. The BG project to the thalamus (Tha) that will in turn send projections to the motor cortex (MCtx). Moreover, the basal ganglia projects to the mesencephalic locomotor region (MLR), which is responsible for the initiation of movement. MLR project to neurons in the reticular formation (RF) in the hindbrain, which in turn project to the spinal networks (CPG's) in the spinal cord. The cerebellum integrates movement-generated somatosensory feedback according to motor behaviour, as well as by modulating the activity in the descending pathways. Somatosensory feedback modulates the activity of the spinal network, this will be further described in section 1.2.3.

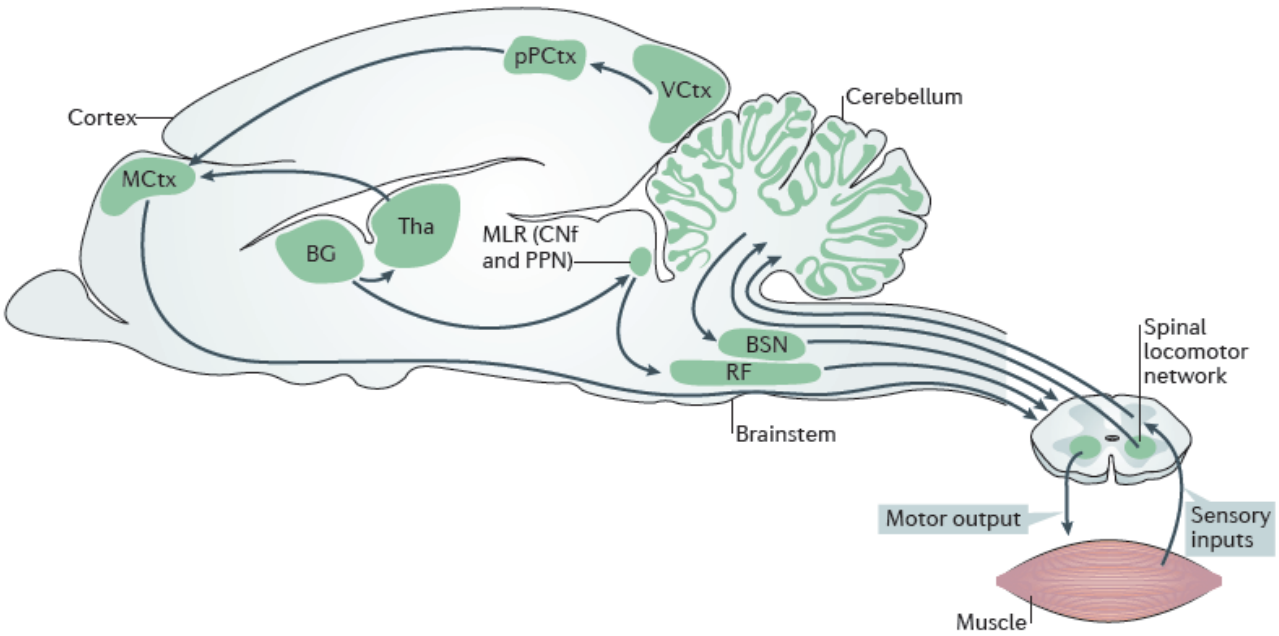

Figure 3. Organization of the supraspinal areas involved in the neural control of locomotion in vertebrates. Adapted with permission from Kiehn (2016). MCtx = motor cortex. MLR = mesencephalic locomotor region. CNf = cuneiform nucleus. PPN = pedunculopontine nucleus. BG = basal ganglia. Tha = thalamus. pPCtx = posterior parietal cortex. VCtx = visual cortex. RF = reticular formation. BSN = brainstem nuclei.

Although the abovementioned presents a general understanding of the supraspinal connectivity for locomotion, some studies have described the involvement of supraspinal centres in upper limb movement, such as rhythmic arm and finger movements. Thus, it has been shown that during unilateral freely chosen middle finger tapping, activation of cortical areas include activation of the contralateral primary motor cortex, the contralateral primary sensory cortex, the supplementary motor area (SMA), and premotor areas (Boecker et al. 1994). This was in line with subsequent findings of internally and externally paced repetitive finger movements (Gerloff et al. 1998). Moreover, it has been suggested that given the important role of the MLR and cerebellum for lower limb movements, they may also be involved in rhythmic arm movements (Zehr et al. 2004). Also, it has been suggested that a reduction in excitability of the primary motor cortex during rhythmic arm movement could reflect a decrease in the contribution of the motor cortex to the generation of rhythmic motor output compared with tonic contractions (Carroll et al. 2006). In continuation, Carroll et al. (2006) further proposed this is likely due to the contribution of spinal CPG's during the rhythmic movement. Furthermore, it has been speculated that if rhythmic movement has been generated, there is possibly a point where the control moves from predominant supraspinal mechanisms towards more predominant spinal mechanisms (Power & Copithorne 2013).

1.2.2 CPG's

The spinal component, termed CPG's, are neuronal networks consisting of specialized spinal interneurons that can produce rhythmic motor patterns in the absence of supraspinal descending drive and sensory feedback (Marder & Bucher 2001, Grillner 2009). The function and morphology of CPG's has been studied extensively in animal preparations (Katz & Harris-Warrick 1990, Cazalets et al. 1992, Kriellaars et al. 1994, Grillner 2003, Iwagaki & Miles 2011, Cropper et al. 2017). Although the existence of CPG's has been proven in several vertebrate species (Lacquaniti et al. 2013), it has been debated whether CPG's are functionally integrated in the control of human movements (Duysens & Van de Crommert 1998). Therefore, it must be noted that the spinal neural control between humans and animals most likely differ due to evolutionary conservations of mechanisms and functions of neural coupling (Zehr et al. 2016). However, it has been argued that the CPG's acts as a component for the generation and modulation of rhythmic movement in humans (Burke et al. 2001, Zehr et al. 2004, Zehr 2005). Moreover, it has been argued that for the generation of stereotyped rhythmic movement, descending input from supraspinal centres likely plays a larger role in humans compared with animals (Solopova et al. 2014, Power et al. 2018, Golowasch 2019). **Figure 4** presents an

illustrative overview of interactions at the spinal level. As such, output from the CPG can act directly on to the motoneuronal pools and indirectly through interneurons on to the motoneuronal pools. Furthermore, input from supraspinal centres can act directly on to the CPG, on interneurons and motoneurons. In addition, afferent feedback arising from the rhythmic movement act directly on to the motoneuronal pools, the interneurons, the CPG as well as the supraspinal centres (Burke et al. 2001, Zehr et al. 2004).

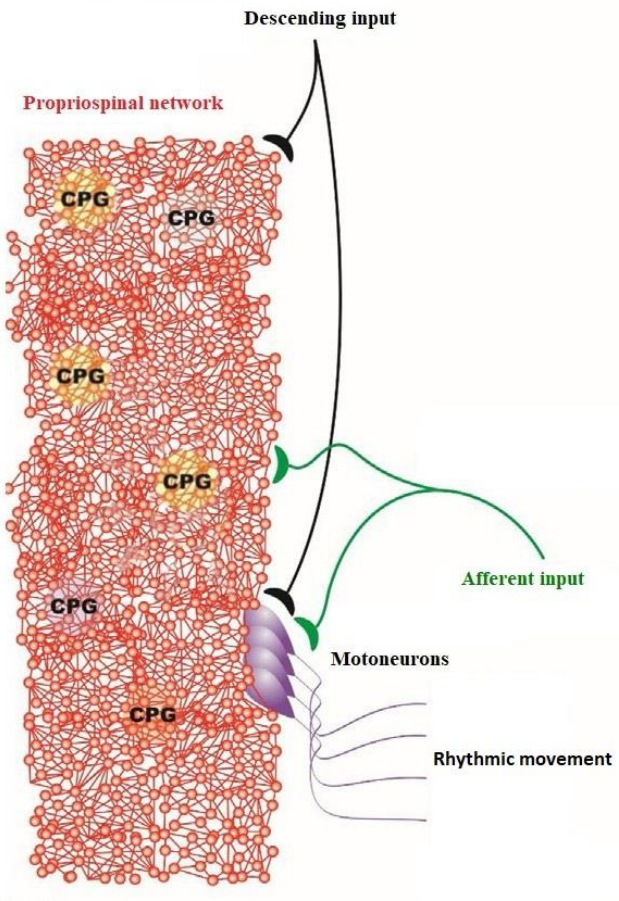

Figure 4. Illustrative overview of the interactions between supraspinal descending input and afferent input at the spinal level on rhythmic movement in humans. Modified with permission from Taccola et al. (2018).

1.2.3 The role of sensory feedback on rhythmic movement

It has been shown that sensory signals plays an important role in how the nervous system adapts and organizes activity that result in rhythmic motor behaviour (Grillner 2009, Frigon 2017). This sensory information is constantly available, particularly through dynamically changing sources such as proprioceptive and cutaneous input, to the spinal cord and cortical areas. As mentioned above and

shown on **Figure 4**, afferent input can act directly on to the motoneuronal pools, the interneurons, the CPG and supraspinal centres via fast-acting neurotransmitters at the pre-synaptic cell (Burke et al. 2001, Grillner 2003). Moreover, sensory feedback provides an input to the nervous system through neuromodulators, that can alter synaptic transmission and thus contribute to the modulation of motor pattern generation and regulation (Grillner 2003, Kettunen et al. 2005, El Manira & Kyriakatos 2010, Marder 2012). Neuromodulators are substances that act as second-messenger signals at the post-synaptic cell, mediating the opening of channels for slow-acting neurotransmission (Nadim & Bucher 2014). Thus, neuromodulators, unlike that of neurotransmitters, does not necessarily carry excitation or inhibition from one neuron to another, but instead alters either the cellular or synaptic properties of certain neurons so that neurotransmission between them is changed (Nadim & Bucher 2014). A wide range of neuromodulators have been described, examples include acetylcholine, dopamine and serotonin, which each can transform the intrinsic properties of circuit neurons (Marder 2012). For example, it has been shown that serotonin can alter the excitability of CPG's in the rat (Cazalets et al. 1992), and more recently it has been proposed that serotonin also can alter the excitability of spinal motoneurons in humans (Wei et al. 2014, Perrier, Cotel 2015). In continuation, it has been shown that the sensory input can influence the CPG, which then selects the appropriate sensory information according to the external requirement (Dietz 2003, Kiehn 2011, Kiehn 2016). Thus, recent studies performed on spinal cord injured humans have shown that the excitability of the spinal circuitry can be modulated with by spinal cord stimulation in combination with pharmacological neuromodulation (Angeli et al. 2014, Gad et al. 2017, Taccola et al. 2018, Gill et al. 2018). Moreover, it has been shown that cortical activity in the primary somatosensory and motor cortex is increased, and hence altered excitability, following afferent input from active finger tapping (Kuboyama et al. 2005), as well as passive finger tapping (Carel et al. 2000, Reddy et al. 2001, Nakagawa et al. 2017).

1.2.4 Behavioural studies on human rhythmic movement

It must be noted that studies in humans are challenged by the restricted access to the spinal cord (Dietz 2003, Zehr 2005). This further implies that direct evidence for the existence of CPG's in humans remain inconclusive. However, studies providing indirect evidence of CPG in humans has been performed in patients with spinal cord injuries (Calancie et al. 1994, Dimitrijevic et al. 1998) and infants (Yang et al. 1998, Dominici et al. 2011). Thus, it is thought that control of rhythmic movement is similar in humans and animals (Duysens & Van de Crommert 1998, Zehr & Duysens 2004, Klarner & Zehr 2018). However, it has been argued that our understanding of the nervous system's

organization and function can be increased through the analysis of motor behaviour (Goulding 2009, Schlinger 2015, Klarner & Zehr 2018). Therefore, scientific approaches in humans are instead dictated to deduce from indirect measurements and observations on the level of the entire system (Klarner & Zehr 2018). Hence, studies on the systemic level provides important understanding of i.e. determining the functional integration of the neural networks in motor programs (Yang et al. 1991, Carroll et al. 2006, Sakamoto et al. 2007, Hundza et al. 2012, Mora-Jensen et al. 2017).

To evaluate possible effects in the human nervous system on motor behaviour in rhythmic movements, several methods and techniques have been applied. These methods include for instance force recordings (De Luca & Erim 1994, Radwin & Ruffalo 1999, Kim et al. 2014, Sardroodian et al. 2016), kinematic recordings (Haken et al. 1985, Sardroodian et al. 2016, Mora-Jensen et al. 2017), recordings of muscle activation (Lee et al. 2009, Piitulainen et al. 2013, Kim et al. 2014, Nakagawa et al. 2017, Sasaki, Ryoki et al. 2018), neurostimulation such as e.g. transcranial magnetic stimulation (TMS) (Pascual-Leone et al. 1995, Carroll et al. 2006, Solopova et al. 2014), imaging techniques such as e.g. functional magnetic resonance imaging (fMRI) (Carel et al. 2000, Cleland & Schindler-Ivens 2018), and the study of motor variability (Vaillancourt & Newell 2002, Stergiou et al. 2006, Faisal et al. 2008, Stergiou & Decker 2011). In addition, both active (Gerloff et al. 1998, Arunachalam et al. 2005, Onishi et al. 2013, Sardroodian et al. 2016) and passive finger movements (Carel et al. 2000, Otsuka et al. 2017, Nakagawa et al. 2017, Tsuiki et al. 2019) has been investigated to elucidate aspects related to the motor control of rhythmic behaviour.

Summarizing the abovementioned, then the freely chosen finger tapping rate is considered to reflect a predominantly CPG-mediated movement, in line with previous suggestions (Hansen & Ohnstad 2008, Shima et al. 2011). Furthermore, applying finger tapping as an exercise model, exploits a movement that is regarded as simple and automated (Kawashima et al. 1999) and which involves only one small body segment. Thus, using unloaded finger tapping movements with minimal influence of external and internal conditions, allows individuals to perform human voluntary stereotyped rhythmic movement at a widespread range of rates, which is of interest in the present project.

1.3 Repeated bout rate enhancement

Curiously, a previous study has demonstrated that the freely chosen tapping rate is increased in the second of two consecutive tapping bouts (Hansen et al. 2015). This behavioural phenomenon has

been termed ‘repeated bout rate enhancement’ (RBRE). Briefly, the study by Hansen et al. (2015) revealed that the freely chosen tapping rate during voluntary index finger tapping was increased following submaximal muscle activation, in form of finger tapping. Thus, four consecutive 3-min bouts, each separated by 10 min rest periods, of unloaded voluntary finger tapping resulted in a cumulating increase in tapping rate, which gradually amounted to a maximum magnitude of on average 8.2%. The phenomenon could possibly be an example of priming, which can be described as a change in behaviour generated by a preceding stimulus (Stoykov & Madhavan 2015). In a follow-up study to the study by Hansen et al. (2015), the phenomenon of RBRE was replicated (Mora-Jensen et al. 2017). In addition, further details on separate effects of the rate enhancement on the movement pattern of the index finger were revealed. Thus, it was shown that the increase in tapping rate was accompanied by a reduction in the index finger’s range of vertical displacement, whereas the tapping force remained unchanged (Mora-Jensen et al. 2017). However, the studies by Hansen et al. (2015) and Mora-Jensen et al. (2017) raised a number of questions about the phenomenon of RBRE. On the basis of the studies by Hansen et al. (2015) and Mora-Jensen et al. (2017), the following three research questions were identified: *i*) Can sensory feedback alone elicit the rate enhancement? *ii*) What is the more exact influence of bout duration on the phenomenon? *iii*) Is it possible to ascribe characteristics between individuals who show or do not show RBRE?

To further address the abovementioned research questions, hypothetically it could be that: *i*) Sensory feedback from proprioceptors and/or cutaneous afferents can alter the net excitability in the central nervous system which in turn could result in a change in the freely chosen tapping rate. This change in excitability could possibly be induced by neuromodulators (El Manira & Kyriakatos 2010, Frigon 2017) acting on to the spinal CPG (Finkel et al. 2014), supraspinal centres (De Luca & Erim 1994), or a combination of both. *ii*) The phenomenon is subjected to a dose-response relationship in proportion to the tapping bout duration. Thus, it has been proposed that neuromodulators can exert effect at different timescales (Nadim & Bucher 2014), with as little as 30 s of electrical stimulation enough to modulate the rhythmic motor output of a CPG (Sánchez & Kirk 2000, Sánchez & Kirk 2002). *iii*) Although RBRE is elicited on the level of a gross group of individuals, it has previously been reported that approximately 1 out of 3 do not show the phenomenon. It is possible that variations in motor control strategies can reflect neural adaptability and flexibility to perform a motor task in an optimal manner (Faisal et al. 2008, Stergiou & Decker 2011). To elucidate differences in motor variability, measures of linear (Stergiou & Decker 2011) and nonlinear (Slifkin & Newell 1999) metrics has been applied to reflect the central nervous systems ability to take benefit of the abundancy

of the motor system (Latash & Anson 2006). Thus, it has been proposed that the capacity to adapt to motor tasks can be investigated by examining how the motor variability in a motor task is expressed by means of biomechanical parameters (Srinivasan & Mathiassen 2012).

1.4 Aims of the Ph.D. project

The overall objective of the Ph.D. project was to increase our understanding of voluntary stereotyped rhythmic movements. More specifically, this project had three main purposes, which was to investigate and further elucidate the phenomenon of RBRE during the task of finger tapping.

The specific aims of the Ph.D. project were:

1. To elucidate whether sensory feedback from passive tapping in itself is sufficient to elicit RBRE (study I).
2. To investigate the effect of tapping bout duration on elicitation of RBRE and rate enhancement (study II).
3. To investigate motor variability in responders and non-responders of RBRE (study III).

In study I, various forms of finger tapping (i.e. freely chosen, passive, and air tapping) were performed to primarily test whether RBRE would be elicited in the absence of descending drive (study I). For study I, an experimental hypothesis was tested, namely whether imposed passive tapping (i.e., imposed sinusoidal tapping like finger movements without requirement of supraspinal drive) would also elicit repeated bout rate enhancement (study I). A confirmatory finding would support a working hypothesis that sensory feedback in itself can elicit RBRE, whereas an unsupportive finding would support a working hypothesis that sensory feedback in itself cannot elicit RBRE.

In study II, various tapping durations, ranging from 20 to 180 s, during the first tapping bout was performed (study II). It was hypothesized that there is a dose-response relationship between the duration of priming and the magnitude of rate enhancement (study II).

In study III, linear and non-linear metrics applied to kinetic and kinematic time series were extracted to investigate motor variability in responders and non-responders of RBRE. It was hypothesized, that responders would perform finger tapping with a lower magnitude of variability and a more complex structure of variability compared with the non-responders (study III).

2 METHODS

The following section provides an overview of the methods and equipment used in this project.

2.1 Subjects

A total of 121 (60 men, 61 women) healthy individuals participated in the three studies (study I-III). An overview of the baseline anthropometric measures, age and number of participants from each study is presented in **Table 1**. For studies I-II, two exclusion criteria were applied, namely: 1) any history of neural or musculoskeletal diseases or disorders, and 2) recent exposure to execution of rhythmic movements with their fingers, such as playing an instrument or playing computer games, more than one hour weekly. Furthermore, the participants were informed not to consume alcohol or euphoric substances during the final 24 hours before testing and not to consume coffee during the final 3 hours before testing. All of the studies conformed to the standards set by the Declaration of Helsinki and the procedures were approved by The North Denmark Region Committee on Health Research Ethics (N-20170017). Written informed consent was obtained from all participants.

Table 1. Characteristics of the participants in studies I-III. The population in study III was partly from study I and II.

	Study		
	I	**II**	**III**
Number of subjects	33 (23 men, 10 women)	88 (37 men, 51 women)	102 (48 men, 54 women)
Age (years)	25.4 ± 3.5	25.6 ± 5.3	25.5 ± 5.0
Height (m)	1.82 ± 0.04	1.74 ± 0.09	1.75 ± 0.09
Body mass (kg)	80.4 ± 12.5	72.7 ± 12.3	74.6 ± 12.7

2.2 Considerations on experimental design

For the present project, some overall considerations regarding the selection criteria and the experimental design were applied.

As the focus of the project considers the effects of rate enhancement, it was decided to investigate participants who showed RBRE. For the selection of participants deemed to elicit RBRE, a criterion of a minimum increase of 3% of the freely chosen tapping rate, from the first to the second

bout, was applied (study I-II). This criterion was based on test-retest data of tapping rates from the original study describing RBRE (Hansen et al. 2015).

Furthermore, it should be noted that subsequent to the selection of participants showing RBRE, the following test sessions reflect rate enhancement as opposed to RBRE. This is a consequence of the experimental design including repeated measures and the fact that rate enhancement is an acute state which presumably cannot be elicited more than once per test session. Thus, the phenomenon of RBRE is used to identify responders and subsequently rate enhancement is evaluated to identify effects of an increased tapping rate.

For the statistical analysis, the first tapping bout in the first tapping session was considered a baseline test (study I-II). Thus, it was assumed that the tapping rate performed in the baseline test reflected the freely chosen tapping rate of each individual, for which the subsequent measurements of rate enhancement would be statistically compared with. With regard to this assumption, it should be noted that although the inter-individual tapping rate is highly individual, the intra-individual tapping rate is robust (Hansen & Ohnstad 2008). Thus, the degree of steadiness of the freely chosen tapping rate is high (i.e. an intra-individual 95% confidence interval of the tapping rate of 13 taps min^{-1} was reported across 7 tests) (Hansen & Ohnstad 2008). Furthermore, a washout period of at least 3-week was imposed to ensure that the freely chosen tapping rate returned to the baseline tapping rate (Hansen & Ohnstad 2008, Hansen et al. 2015, Sardroodian et al. 2016).

2.2.1 Finger tapping test sessions

For studies I-II, finger tapping was performed during the test sessions. In total, three different forms of finger tapping were used. The three forms of tapping included, freely chosen, imposed passive, and tapping in the air (air tapping). It applies to all three forms, that tapping was performed with the right index finger, while the remaining four fingers of the right hand were in an extended position and resting state on the table.

Each test session was commenced with a demonstration of how to perform the finger tapping, in addition to an explanation of the test procedure in general. During all tests sessions, the participant assumed a standardized test position. Thus, the participant was instructed to sit in a chair in front of a table. The participant was then instructed to keep the palm of the right hand flat on the table. The participant's back was straight, while the lower arm was resting on the table. It applies to all test sessions that the participant reported to the laboratory at the same time of the day, to avoid possible

circadian rhythm effects on the results (Moussay et al. 2002). In addition, there was no warm-up or familiarization before testing, to prevent any form of rate enhancement before the first tapping bout.

2.2.1.1 Freely chosen tapping

In studies I-II, the freely chosen finger tapping rate was measured. For the freely chosen tapping, it was emphasized that the tapping was not required to be performed as fast as possible or at a constant rate, but rather at the participant's "own individual preferred rhythm" while at the same time "thinking about something else."

2.2.1.2 Passive tapping

In studies I-II, passive finger tapping was applied by a custom-built machine, see ***Figure 5***. For the passive tapping, the right index finger was in a relaxed state. The tip of the index finger was placed at the end of a rocker arm, so that the machine could provide passive extension–flexion movement of the finger in the vertical plane. The participant was instructed to "relax as much as possible".

Figure 5. Illustration of the custom-built machine used to apply passive tapping in studies I-II. Adopted from study I (Emanuelsen et al. 2018).

2.2.1.3 Air tapping

In study I, tapping like-movements in the air was measured at a freely chosen tapping rate. For the air tapping, the participant was instructed to assume the test position in which the table supported all fingers but the index finger. Thus, the index finger had free range of motion within a hole in the table. Then, the participant was instructed to perform the tapping as described in the freely chosen tapping.

2.2.1.4 Tapping bout durations

In study I, the duration of all tapping bouts was 180 s. However, in study II various tapping bout durations were used to act as priming during the first tapping bout. These tapping durations included 20, 60, 120, and 180 s of priming.

2.3 Data collection

An overview of the used methods and equipment in all studies is summarized in **Table 2**. The applied methods and equipment include recordings of force, kinematics, surface electromyography (sEMG), and electroencephalography (EEG). Briefly, the force and kinematic recordings were included to evaluate characteristics of the movement pattern during voluntary finger tapping. sEMG recordings was included to verify that the passive tapping sessions were performed as intended and to evaluate effects of muscle activation during the various forms of finger tapping performed. EEG recordings was included to perform a qualitative analysis of sensory evoked potential (SEP) responses of somatosensory feedback of the various tapping forms. The methods and equipment will be presented in the following section.

Table 2. Overview of the used methods used for data collection in all three studies.

	Study		
	I	**II**	**III**
Force recordings	X	X	X
Vertical fingertip displacement	X	X	X
Custom-built machine for passive finger tapping	X	X	
Surface electromyography (sEMG)	X		
Electroencephalography (EEG)	X		

2.3.1 Force recordings

For studies I-II, the vertical tapping force was recorded, during all tapping bouts with freely chosen tapping, using a force transducer (FS6-250, AMTI, Watertown, MA, USA). The force signal was amplified, analogue low-pass filtered, and digitalized using a NI BNC-2090A A/D-board (National Instruments, Austin, TX, United States). The force recordings were then digitally low-pass filtered. The recordings were sampled using a Lab-VIEW-based (National Instruments Co., Austin, TX, United States) custom-programmed software (Mr. Kick III software, Aalborg University, Aalborg, Denmark). For further details, the reader is referred to studies I-II.

In study I, the participants performed maximal voluntary contractions (MVCs) on the force transducer. MVCs were performed as isometric index finger extension (i.e. maximal lifting of the finger, which was strapped on to the transducer) and index finger flexion (i.e. maximal pressing on to the transducer). For both conditions, three 5-s MVC trials was performed. For this, the participant was instructed to gradually increase the force to a maximum during the first 3 s and then maintain the force for an additional 2 s. All MVCs were separated by 1-min rest. For further details, the reader is referred to study I.

2.3.2 Vertical fingertip displacement

For studies I-II, the vertical displacement of the right index fingertip was recorded during all tapping bouts, using a motion capture system (Standard VZ-4000v, Phoenix Technologies Inc., Burnaby, BC, Canada). For this, a LED-tracker was attached to the participant's nail of the index fingertip (study I-II). The kinematic recordings were sampled using VZSoft software™ (Phoenix Technologies Inc.,

Burnaby, BC, Canada). An output trigger from the motion capture system was used to synchronize the force recordings. For further details, the reader is referred to studies I-II.

2.3.3 Electromyographic recordings

In study I, sEMG was recorded from the flexor digitorum superficialis (FDS) muscle and extensor digitorum communis (EDC) muscle on the right arm. The motor point of the respective muscles were identified using a DISA electrostimulation device (Type 9014E0102, DISA Elektronik, Herlev, Denmark). The participant's skin over the identified motor points was shaved, abraded and cleaned with alcohol, according to the SENIAM recommendations (Hermens et al. 2000). Then, two sEMG electrodes were mounted over the motor points, using a 2 cm inter-electrode distance. Finally, a reference electrode was placed over the lateral epicondyle of the humerus. Prior to the tapping bouts, background sEMG was recorded for 5 s in a relaxed state. Then, sEMG was recorded during the entire duration of the tapping bouts. For further details, the reader is referred to study I.

For the recordings of sEMG data, the signals were pre-amplified and then the signals were recorded using a custom programmed software (Mr. Kick III software, Aalborg University, Aalborg, Denmark). The sEMG signals were analogue band-pass filtered, A/D converted using a NI BNC-2090A A/D-board (National Instruments, Austin, TX, United States), and then sampled. For further details, the reader is referred to study I.

2.3.4 Sensory evoked potentials (SEPs)

In study I, SEP responses were recorded during tapping using a custom programmed software (Mr. Kick III software, Aalborg University, Aalborg, Denmark). First, the participant was rubbed with abrasive gel on the CP3 position in the 10-20 system (Trans Cranial Technologies 2012), on a reference point at the right earlobe, and a ground reference point at the forehead. Then, a monopolar disc electrode was placed at each position using a conductive paste (study I). For the recordings, the SEP signals were amplified and band-pass filtered using a 4^{th}-order Butterworth filter, respectively. The signals were A/D converted using a 12 bits NI BNC-2090A A/D-board (National Instruments, Austin, TX, United States) (study I). The SEP averaging during the finger tapping was triggered by the rising edge on the force signal (during freely chosen tapping) and on the basis of the kinematic signal (during passive and air tapping). Each cycle was initiated when the fingertip was at its lowest point during each tap. For further details, the reader is referred to study I.

2.4 Data analysis

An overview of the reported variables in all studies is summarized in **Table 3**.

Table 3. Overview of the reported variables in studies (I-III).

	Study		
	(I)	**(II)**	**(III)**
Tapping rate (taps min^{-1})	X	X	X
Peak force (N)	X	X	X
Time to peak force (ms)	X	X	
Duration of finger contact phase (ms)	X	X	
Vertical displacement (mm)	X	X	X
Maximal voluntary electromyography (%MVE)	X		
Sensory evoked potentials (uV)	X		
Standard deviation of vertical force (N)			X
Standard deviation of vertical displacement (mm)			X
Coefficient of variation of vertical force (%)			X
Coefficient of variation of vertical displacement (%)			X
Sample entropy of vertical force			X
Sample entropy of vertical displacement			X

2.4.1 Force recordings

For studies I-II, the force recordings were analysed using MATLAB version R2013a (The MathWorks, Inc., Natick, MA, USA). For this analysis, a custom-written MATLAB script was used. A baseline force value was determined as the mean force across 1 s before tapping started. After the recording, the baseline output was subtracted from the signal obtained for each tap during the tapping bout. The initiation of each tap was determined as the last time the signal crossed the baseline force value before the force increased because of finger contact. The end of the finger contact phase was determined as the first time the force decreased below the baseline force value again, following the finger contact. For a representative example of a force profile from a single finger tap, see **Figure 6**.

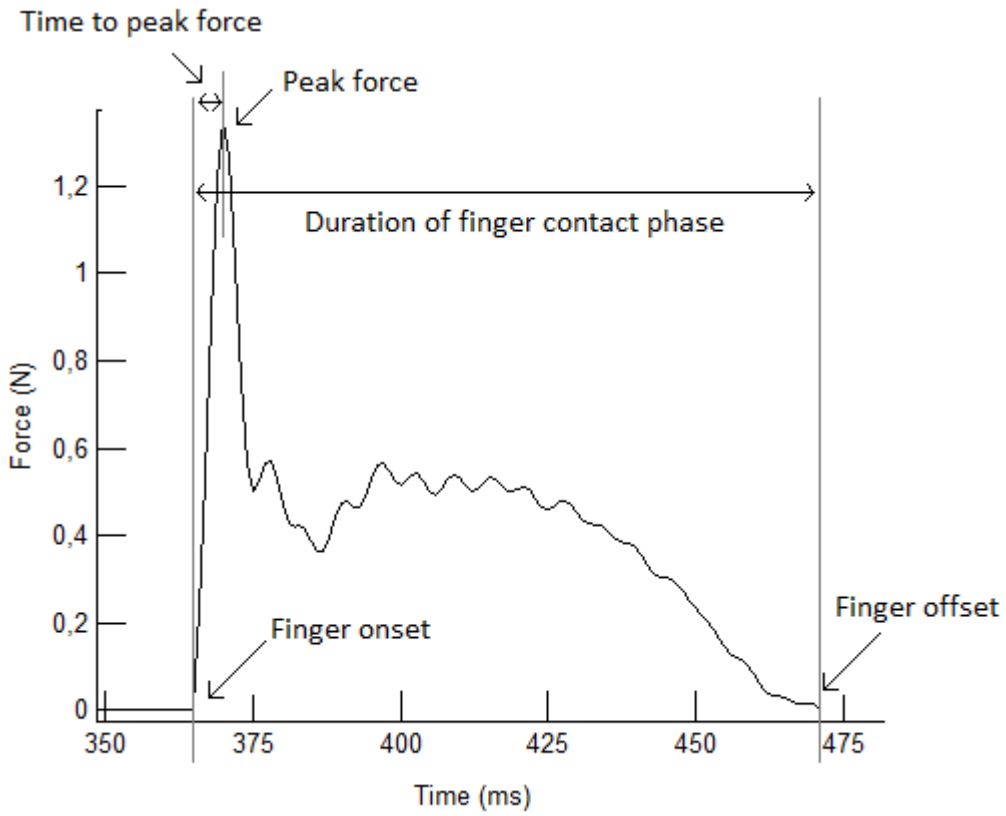

Figure 6. Representative example of a force profile from a single finger tap. Key events and characteristics used to calculate force variables are superimposed on the force profile.

For studies I-II, the following four variables were extracted on a tap-to-tap basis for each tapping bout and computed as averages across an entire tapping bout prior to statistical analyses: (*i*) Tapping rate (in taps min^{-1}) was calculated as 60 s divided by the elapsed time (in s) between two consecutive force onsets. (*ii*) Peak force (in N) was determined as the difference between the maximal force value detected during the contact time and the baseline force value. (*iii*) Time to peak force (in ms) was determined as the time from the force onset to the peak force during each tap. (*iv*) Duration of finger contact phase (in ms) was determined as the time from the force onset to the force offset. For further details, the reader is referred to studies I-II.

The force signals recorded during the MVC trials in study I were smoothed with a running average using 100 ms intervals with no overlap. Subsequently the highest force value from each trial was determined. The largest of these three force values was used for normalization of force recorded during tapping. For further details, the reader is referred to study I.

2.4.2 Vertical fingertip displacement

For studies I-II, the kinematic data were analysed using a custom-written MATLAB script, used to detect local minima and maxima on the position trace across the entire duration of the tapping bouts. For the freely chosen and air tapping conditions, the vertical displacement (mm) was calculated by subtracting the minimum value from the maximum value for each tap, determined by the force trace. For the passive tapping condition, vertical displacement was calculated by subtracting the minimum value from the maximum value for each tap, determined by the position trace. Averaged values of vertical displacement across the bouts were computed prior to statistical analyses. For further details, the reader is referred to studies I-II.

2.4.3 sEMG data processing

In study I, the sEMGs were analysed using a custom-written MATLAB script. Here, the sEMG signals were digitally band-pass filtered using a 4^{th}-order Butterworth filter. The use of sEMG is challenged by inter- and intraindividual differences in conductivity, which can be solved using a normalization procedure (Kasprisin & Grabiner 1998). Thus, sEMG data in study I was normalized with respect to maximum voluntary electromyography (MVE). For this, root mean square (RMS) values of the recordings of background sEMG were computed and averaged across the 5 s recording. For each of the three MVC trials of flexion and extension, respectively, the maximal RMS-value was computed. Then, the highest of the three maximal RMS-values were used for further calculations and termed MVE. For each single tap performed during the tapping bouts, RMS-values were computed and then average values were calculated across each tap. Then, the background sEMG was subtracted. Finally, the values were normalized with respect to the MVE values, averaged across all taps in each 3-min tapping bout and presented as %MVE. For further details, the reader is referred to study I.

2.4.4 Sensory evoked potentials

In study I, the EEG epochs were identified using a custom-written MATLAB script. The analysis time window adopted was the first 100 ms after the trigger. Electrooculograms (EOGs) were rejected by visual inspection of the individual epochs. For visualization, the epochs from each individual tapping bout were filtered with a boxcar moving average, and ‘grand averages’ across participants for each situation were calculated. For further details, the reader is referred to study I.

2.4.5 Calculation of variables of motor variability

In study III, tapping rate and measures of variability of force and kinematics data, respectively, were analysed using a custom-written MATLAB script. For this, the tapping rate was computed as the average tapping rate, extracted from the force recordings, from three 8-s epochs, representing the start, mid, and end of a tapping bout. Then, force and kinematics data were extracted from the same 8-s epochs. Variables of variability, namely the standard deviation (SD), coefficient of variation (CV), and sample entropy (SaEn) were computed from the three 8-s epochs. SaEn was computed using an embedding dimension of m = 2 and a tolerance distances of 0.20×SD. Then, variables of variability were calculated as average values across each epoch. For further details, the reader is referred to study III.

3 RESULTS

This section presents a summary of the main findings of the present Ph.D. project. For further details, the reader is referred to the original articles/manuscripts (Study I-III).

3.1 Elicitation of RBRE on a gross group level (Study I-II)

It applies to both study I and II, that the freely chosen tapping rate was increased from the first bout to the second bout in the baseline tapping session for the gross group of participants ($p = 0.002$ and $p < 0.001$, respectively). The relative magnitude of RBRE corresponded to 7.7 ± 21.1% in study I and 7.9 ± 12.2% in study II. Thus, RBRE was elicited on the level of the gross group of participants in both studies. The average increase in tapping rate in the baseline tapping session in studies I-II is presented in **Figure 7**.

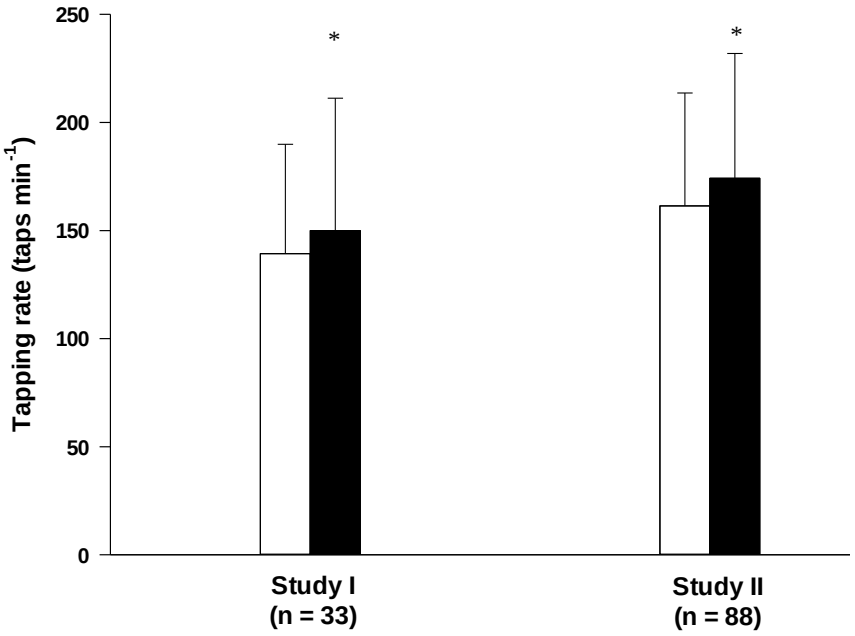

Figure 7. Average tapping rates (+ SD) from the baseline tapping session in study I and study II. The figure reflects RBRE for both study I and II. White bars represent the first tapping bout in each session. Black bars represent the second tapping bout in each session. *Different from the first tapping bout ($p < 0.05$).

The participants who showed RBRE were then selected for participation in additional test sessions, which also included passive (study I-II) and air tapping (study I). In the following results

section, only results from participants demonstrating RBRE is presented. Furthermore, it applies to the following results section, that the analyses of tapping rate, tapping force and vertical displacement was performed from the first bout in the baseline tapping session to the second bout in tapping sessions including freely chosen, passive, and air tapping, respectively.

3.2 Tapping rate (Study I-II)

In study I, rate enhancement was observed following 180 s of priming of freely chosen, passive, and air tapping ($p < 0.001$, $p = 0.001$, and $p = 0.005$, respectively). In study II, rate enhancement was also observed following 180 s of priming of freely chosen and passive tapping ($p < 0.001$ and $p< 0.001$, respectively), see **Figure 8**.

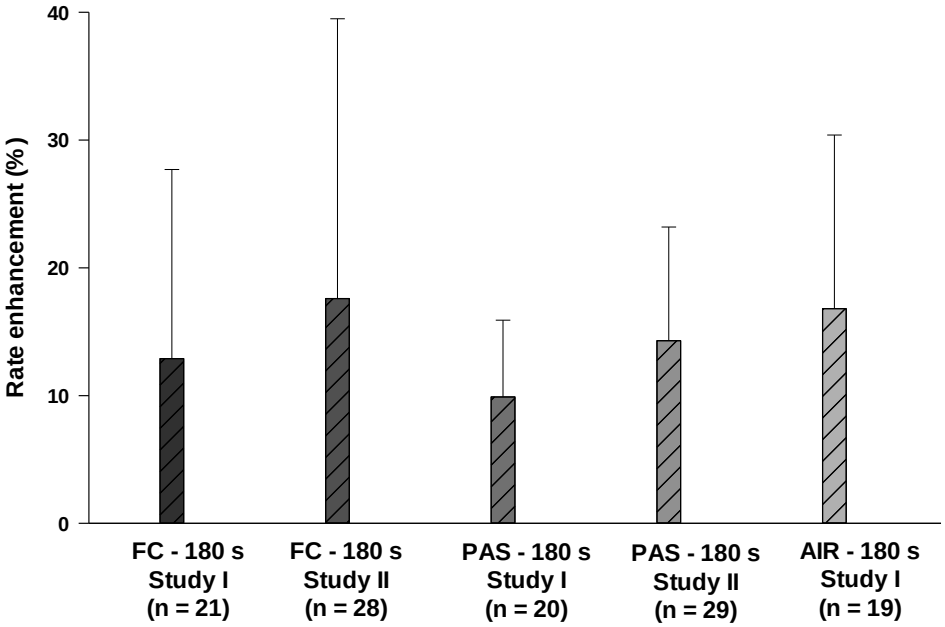

Figure 8. Results of the average relative rate enhancement (+ SD) following 180 s of priming from participants who showed RBRE in study I and study II. FC = freely chosen tapping, PAS = following passive tapping, AIR = following air tapping. All were statistically significant from the baseline tapping session ($p < 0.05$).

In study II, additional tapping sessions applying tapping durations ranging from 20 to 120 s of freely chosen and passive tapping, during the first tapping bout was performed. A two-way repeated measures mixed ANOVA revealed that rate enhancement from the first bout in the baseline tapping session to the second bout in sessions applying 20, 60, and 120 s of priming occurred ($p < 0.001$, $p <$

0.001, and $p < 0.001$, respectively), however there was no difference between the groups ($p = 0.734$) (study II). The average relative rate enhancement following tapping sessions applying 20, 60 and 120 s of priming is presented in **Figure 9**.

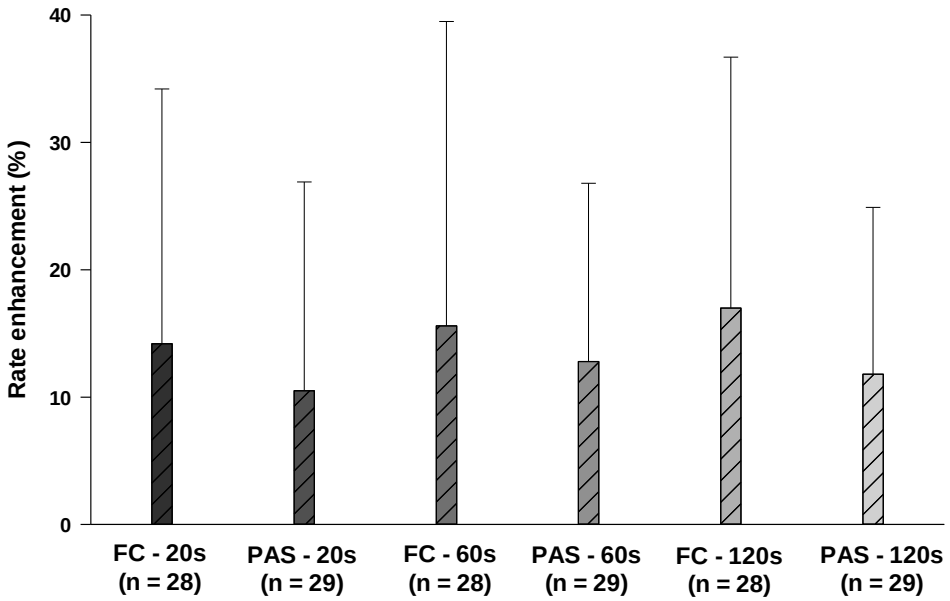

Figure 9. Results of the average relative rate enhancement (+ SD) from participants who showed RBRE in study II, following either 20, 60, or 120 s of priming in the form of freely chosen and passive tapping. FC = following freely chosen tapping, PAS = following passive tapping. All were statistically significant from the baseline tapping session ($p < 0.05$).

3.3 Reliability of the freely chosen tapping rate (Study II)

In study II, a between-day reliability test of the freely chosen tapping rate was performed by calculation of intraclass correlation coefficient (ICC), using a two-way mixed model for absolute agreement ($ICC_{3,1}$). For this, the freely chosen tapping rate in first bout in the baseline tapping session versus the freely chosen tapping rate in the first tapping session applying 180 s of priming was compared. The between-day reliability of the freely chosen tapping rate was high (0.85, $p < 0.001$) (study II).

3.4 Effect of rate enhancement on tapping force (Study I-II)

In study I, the peak force decreased following 180 s of priming in the form of freely chosen and passive tapping ($p = 0.006$ and $p = 0.008$, respectively), see **Figure 10**. The difference in peak force

following freely chosen tapping was not significantly different from the difference following passive tapping (p = 0.794) (study I).

In study II, there was a significant effect of *session* on the absolute values of peak force. The post hoc analysis revealed that the peak force decreased following 180 s of priming (p = 0.007), however there was no difference between the groups (p = 0.854) (study II), see **Figure 10**.

For both study I and II, no changes in either time to peak force or duration of finger contact phase was observed.

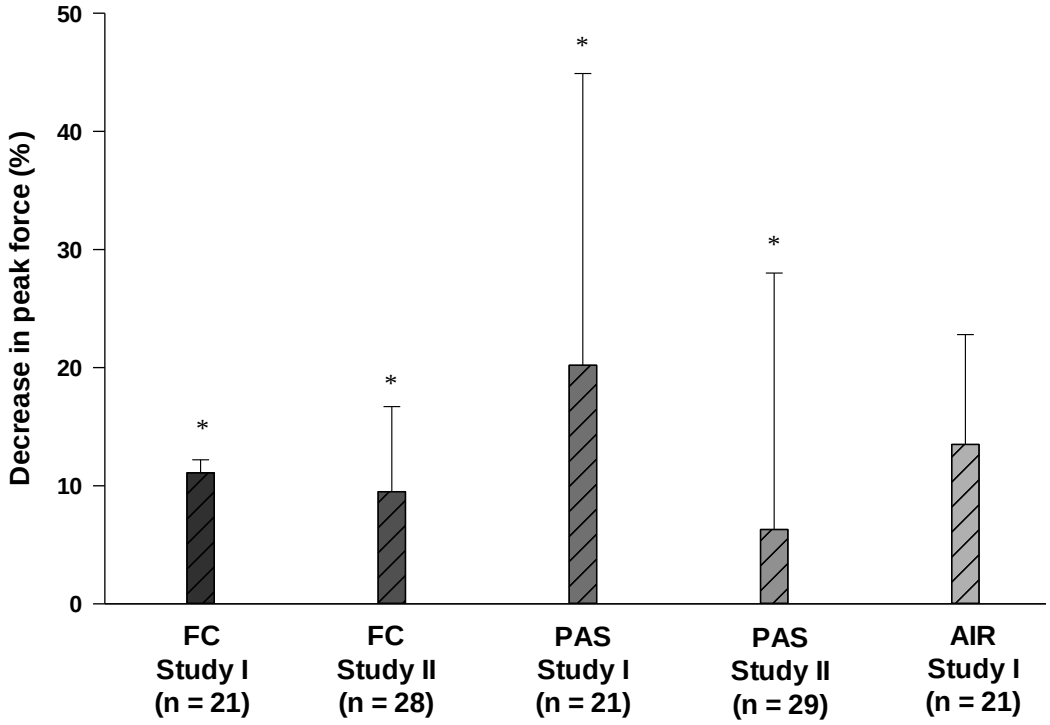

Figure 10. Results of the average relative decrease in peak force (+ SD) following 180 s of priming from participants who showed RBRE in study I and study II. FC = following freely chosen tapping, PAS = following passive tapping, AIR = following air tapping. *Statistically significant from the baseline tapping session (p < 0.05).

3.5 Effect of rate enhancement on vertical displacement of the fingertip (Study I-II)

In study I, the vertical displacement of the fingertip decreased following 180 s of priming in the form of freely chosen and passive tapping (p = 0.019 and p = 0.010, respectively), see **Figure 11**. The difference in vertical displacement following freely chosen tapping was not significant from the

difference following passive tapping (p = 0.780) (study I). In study II, no significant changes in the vertical displacement of the fingertip was observed.

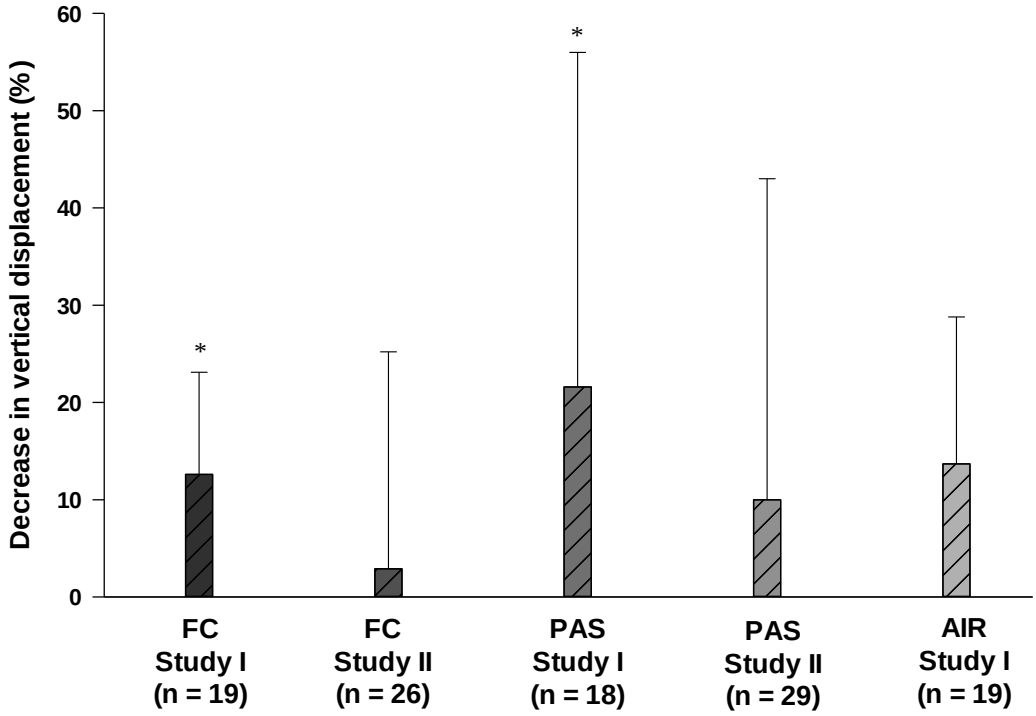

Figure 11. Results of the average relative decrease in vertical displacement of the fingertip (+ SD) following 180 s of priming from participants who showed RBRE in study I and study II. FC = following freely chosen tapping, PAS = following passive tapping, AIR = following air tapping. *Statistically significant from the baseline tapping session ($p < 0.05$).

3.6 Effect of rate enhancement on muscle activation (Study I)

In study I, sEMG was recorded in two separate experiments, namely Experiment 1 and Experiment 2. In Experiment 1, sEMG was recorded to measure the amount of muscle activation during voluntary finger tapping and to evaluate whether participants performed the passive tapping as intended. In Experiment 2, sEMG was recorded to test whether the sEMG method in Experiment 1 was sufficiently sensitive to detect a similar difference in muscle activation during volitional pre-set finger tapping rates, which corresponded to the magnitude of rate enhancement observed in Experiment 1.

In Experiment 1 in study I, the amount of muscle activation was not different between tapping bouts performed at freely chosen tapping rate for both the EDC and FDS muscle (p = 0.361 and p = 0.379, respectively), see **Figure 12**. The amount of muscle activation was significantly lower during

passive tapping compared to freely chosen tapping for both the EDC and FDS muscle ($p = 0.003$ and $p < 0.001$, respectively). Also, the amount of muscle activation was significantly higher during air tapping compared to freely chosen tapping for both the EDC and FDS muscle ($p = 0.038$ and $p < 0.001$, respectively) (study I). Of note, the general sEMG levels were higher in the EDC muscle compared with the FDS muscle, see **Figure 12**. A possible explanation may be that the extension movement must overcome passive elastic resistance in the flexors, whereas the flexion movement is partly due to elastic recoil.

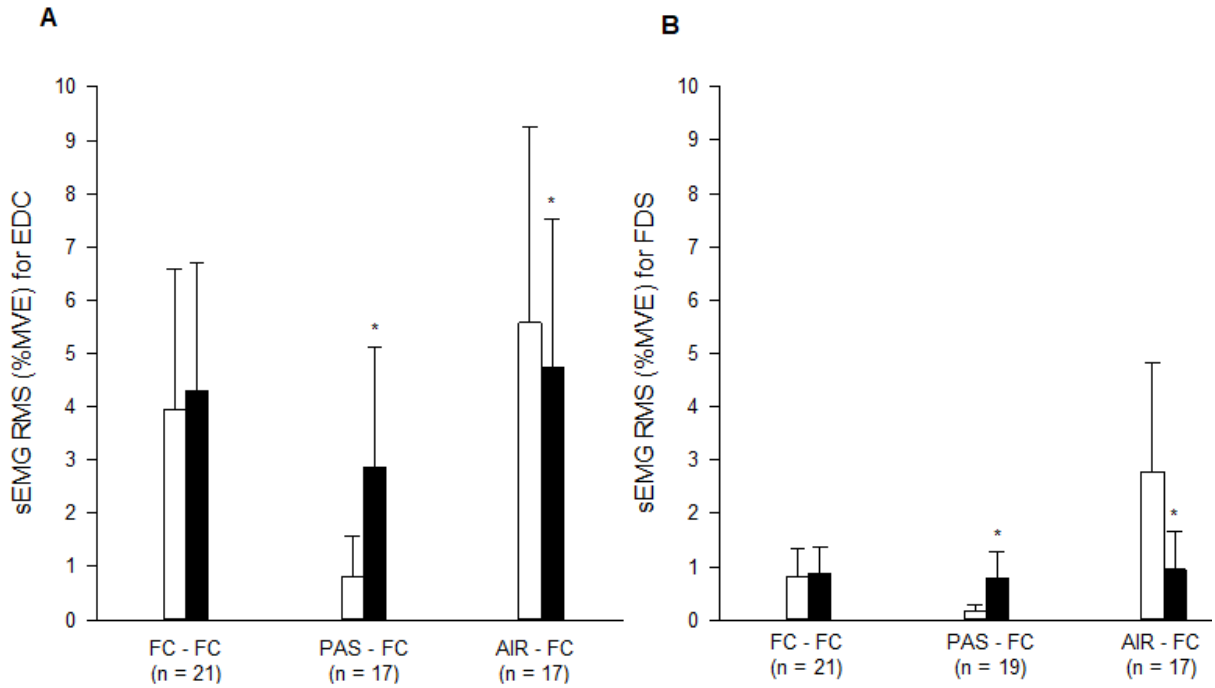

Figure 12. Data of muscle activation from Experiment 1 in study I presented as average + SD %MVE. Panel (A) represents data for the EDC muscle. Panel (B) represents data for the FDS muscle. White bars represent the first bout. Black bars represent the second bout. FC = freely chosen tapping, PAS = passive tapping, AIR = air tapping. *Different from the first bout in the same session ($p < 0.05$). Modified from study I (Emanuelsen, Anders et al. 2018).

In Experiment 2 in study I, participants performed pre-set tapping in two separate bouts, in a counterbalanced order, at 150 and 168 taps min^{-1}, respectively. For the EDC muscle, the amount of muscle activation when tapping at 168 taps min^{-1} was higher compared to tapping at 150 taps min^{-1} ($p = 0.003$) (study I). There was no difference for the FDS muscle ($p = 0.419$), see **Figure 13**.

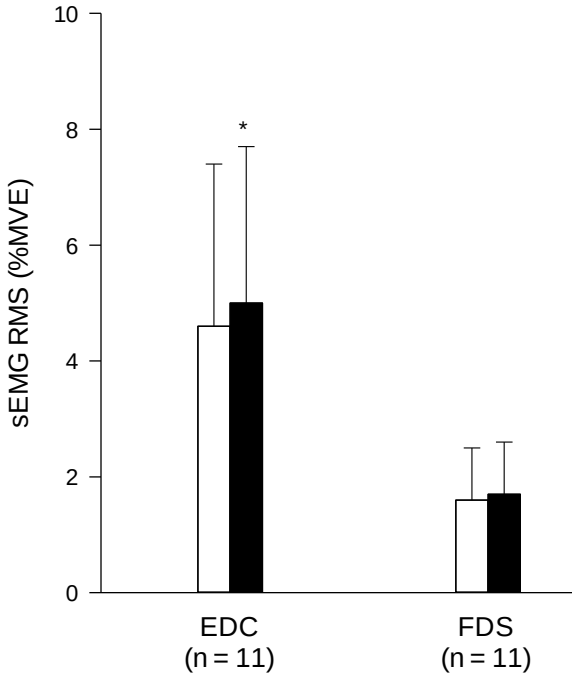

Figure 13. Data of muscle activation from the EDC and FDS muscle during pre-set tapping in Experiment 2 in study I, presented as average + SD %MVE. White bars represent the bout applying 150 taps min^{-1}. Black bars represent the bout applying 168 taps min^{-1}. *Different from the first bout ($p = 0.003$).

3.7 Sensory evoked potentials (SEPs) (Study I)

In study I, grand averages of SEP responses measured during freely chosen, passive and air tapping demonstrated different characteristics in the somatosensory feedback input to the CP3 position, see **Figure 14**. The freely chosen tapping situation showed a triphasic pattern, resembling a pattern elicited by air puff to the tip of the finger previously reported (Hashimoto et al. 1990). This pattern was more pronounced when tapping at a low rate compared with a higher tapping rate, however the pattern at high tapping rate still had resemblance to the pattern presented by Hashimoto et al. (1990). During the passive and air tapping situation, no consistent patterns were observed. It could be assumed that the impact of the fingertip on to the force transducer, during freely chosen tapping, likely elicits a more synchronous afferent burst in combination with the background afferent activity from the movement itself. Thus, the synchronous afferent burst elicits evoked related potentials resembling the triphasic SEPs elicited with air puffs, whereas the passive and air tapping situation merely generates a more diffuse afferent picture.

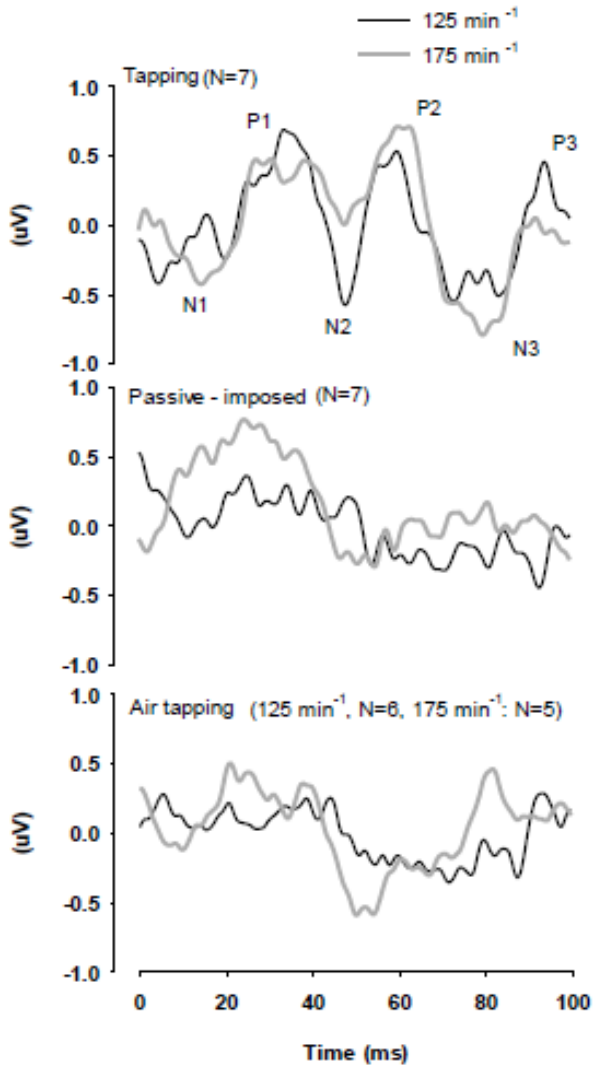

Figure 14. Grand averages of EEG responses during tasks of freely chosen tapping (upper row), passive tapping (mid row) and air tapping (lower row). The profiles represent grand averages across 297 ± 68 artefact-free taps per tapping bout, across participants. The number of participants for each task is indicated in the figure. The time 0 ms corresponds to time of impact (during tapping) and maximal finger flexion (during passive tapping and air tapping). P1, P2, and P3 indicate successive positive peaks. N1, N2, and N3 indicate successive negative peaks. Modified from study I, (Emanuelsen et al. 2018).

3.8 Measures of variability (Study III)

Following data acquisition in study I and II, study III investigated motor variability in individuals who showed (responders) and did not show (non-responders) RBRE in study I and II. For this, the

SD, CV and SaEn from the kinetic (vertical force) and kinematic (vertical displacement) recordings were analysed using a three-way repeated measures ANOVA. In the following results section, only significant findings between groups and bouts will be presented, for further detail the reader is referred to study III.

On an overall group level, the SD of vertical displacement was on average 6.6% lower in the second bout compared with the first bout ($p < 0.001$) (study III). SD of vertical displacement is presented in **Figure 15**.

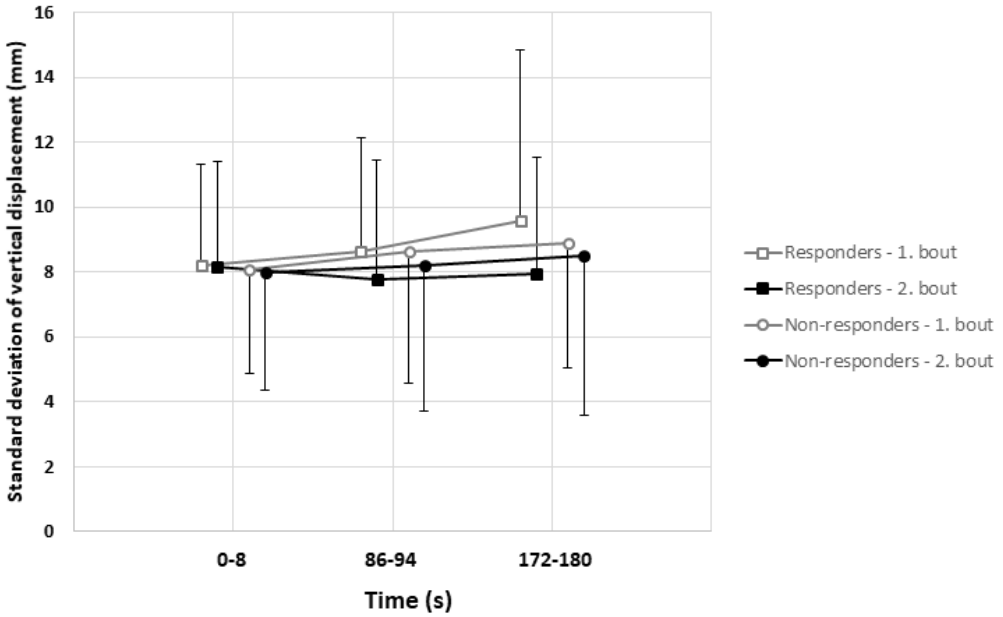

Figure 15. Standard deviation (±SD) of vertical displacement (mm) during the start (0-8 s), the middle (86-94 s), and the end (172-180 s) of each tapping bout, for both responders (n = 68) and non-responders (n = 34). For clearness, data points have been horizontally staggered and ascending and descending SD bars have been removed for the non-responders and responders, respectively. Modified from study III (Emanuelsen et al. 2019).

The SaEn of vertical displacement was on average 13.6% higher for the responders compared with the non-responders ($p = 0.046$). In addition, the SaEn of vertical displacement was on average 6.2% higher in the second bout compared with the first bout for the responders ($p = 0.001$) (study III).

On an overall group level, the SaEn of vertical force was on average 6.0% higher in the second bout compared with the first bout ($p = 0.009$). In addition, the SaEn of vertical force was on average

17.4% higher in the second bout compared with the first bout for the responders ($p < 0.001$) (study III). SaEn of vertical force and displacement is presented in **Figure 16**.

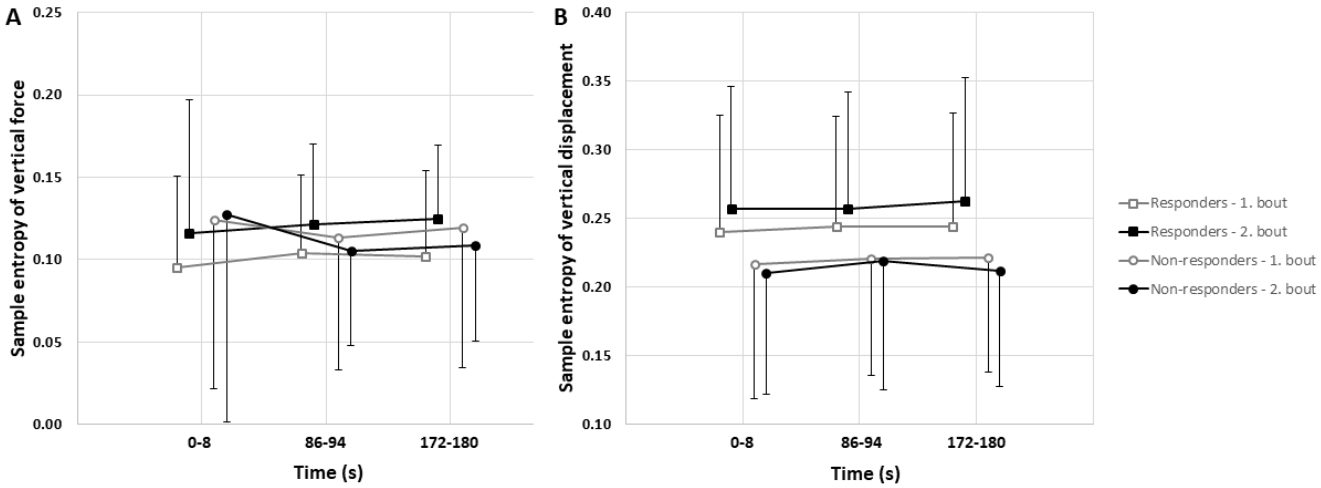

Figure 16. Sample entropy (±SD) of vertical force (panel A) and displacement (panel B) during the start (0-8 s), the middle (86-94 s), and the end (172-180 s) of each tapping bout, for both responders (n = 68) and non-responders (n = 34). Modified from study III (Emanuelsen et al. 2019).

4 DISCUSSION

The aim of the present thesis was to increase our understanding of voluntary stereotyped rhythmic movements, with a main purpose to investigate and further elucidate the phenomenon of RBRE. To this extent, three studies were carried out. The main findings of the three studies were as follows: Study I revealed that RBRE was elicited by various types of finger tapping, including freely chosen, passive, and air tapping. An experimental hypothesis was developed to test whether imposed passive tapping could elicit RBRE, where an affirmative finding would support the working hypothesis that sensory feedback in itself is sufficient to elicit RBRE, whereas an unsupportive finding would reject that sensory feedback is sufficient to elicit RBRE. Thus, the elicitation of RBRE following passive tapping could indicate that sensory feedback in itself is sufficient to elicit RBRE. Two supportive experiments were performed, in which it was demonstrated that RBRE occurred in the absence of an increase in muscle activation. Furthermore, it was demonstrated that rate enhancement occurred regardless of dissimilar prior sensory feedback to the motor cortex. Study II revealed that rate enhancement was elicited independently of the duration of the first tapping bout, using a range of tapping durations from 20 s to 180 s. It was hypothesized that there is a dose-response relationship between the duration of priming and the magnitude of rate enhancement, and that more than 20 s of priming would be required to elicit rate enhancement. Contrary to what was hypothesized, the study showed that a duration of as little as 20 s is sufficient to elicit rate enhancement, in the form of both freely chosen and passive tapping. Study III revealed differences in characteristics of motor variability between individuals who showed or did not show RBRE during study I and II. It was hypothesized that differences in the magnitude (SD and CV) and structure (SaEn) of motor variability between responders and non-responders of RBRE would be present. Contrary to the hypothesis no differences in the magnitude of motor variability was found, however a common observation was that responders and non-responders exhibited different characteristics in the structure of motor variability. Thus, it was demonstrated that the SaEn of vertical displacement was higher for the responders than non-responders. In addition, that the SaEn of vertical force and displacement was higher in the second bout compared to the first bout for the responders. The present results could be a reflection of differences in the dynamics of finger tapping between responders and non-responders. Furthermore, the findings could indicate a greater adaptability to the motor task of finger tapping for the responders compared with the non-responders.

The following chapter will provide an in-depth and more detailed discussion of the main findings, in addition to limitations and perspectives of the present thesis.

4.1 Elicitation of RBRE and effect of freely chosen tapping

In studies I-II, RBRE was elicited on the level of the gross group of participants, following tapping bouts including freely chosen tapping as priming. Accordingly, the relative magnitude of RBRE in study I and II of 7.7% and 7.9%, respectively, were similar and furthermore in line with previous studies reporting relative magnitudes of RBRE of 8.2% and 6.0%, respectively (Hansen et al. 2015, Mora-Jensen et al. 2017). Thus, the present findings in study I and II replicated the phenomenon of RBRE. In relation to the underlying neural mechanisms regulating rhythmic movement (see **Figure 1** and **Figure 2**), it has been proposed that three possible scenarios may be responsible for the regulation of a CPG-controlled movement rate output (Hansen et al. 2015). The three scenarios include 1) increased excitation of supraspinal centres may cause an increase in supraspinal descending central drive (De Luca & Erim 1994, Prochazka & Yakovenko 2007), 2) increased excitation of the spinal CPG itself (Finkel et al. 2014), or 3) a combination of increased excitability of supraspinal and spinal components. Accordingly, the present findings could be interpreted to be a reflection of any of the three scenarios.

4.1.1 Effect of passive tapping on rate enhancement

In study I, priming was also performed in the form of passive tapping to remove the requirement of descending supraspinal drive. The findings in study I revealed that rate enhancement was elicited following priming with passive tapping, for participants who previously showed RBRE. This finding was replicated in study II, see **Figure 8**. The finding, indicating that passive tapping is sufficient to elicit rate enhancement, provided new details on the possible underlying neural mechanisms regulating RBRE. Thus, it could be speculated that peripheral sensory feedback during passive tapping was sufficient to increase the net excitability of the spinal CPG itself that potentially can results in an enhanced motor output, observed as an increase in tapping rate. This notion is supported by the suggestion that the excitability of spinal CPG's in decerebrated and spinal animals can be altered by electrical stimulation of afferents (Edgerton et al. 2008, Etlin et al. 2010, Finkel et al. 2014) and through pharmacological neuromodulation (Katz & Harris-Warrick 1990, Chapman & Sillar 2007). In addition, studies on spinal cord injured humans have shown that a combination of pharmacological neuromodulation and spinal cord stimulation results in excitation of the spinal circuitry (Angeli et al. 2014, Gad et al. 2017).

It is also possible that peripheral sensory feedback during passive tapping, projecting to supraspinal centres, caused an excitation of supraspinal centres (i.e. SMA, primary MCtx) (Reddy et al. 2001, Onishi et al. 2013, Nakagawa et al. 2017). A net excitation of supraspinal centres may cause an increase in descending central drive (Prochazka & Yakovenko 2007) which potentially can result in an enhanced motor output of CPG-controlled movement, thus resulting in an increase in tapping rate. This is further supported by the finding that passive movements, compared to rest, has been reported to show activation of most of the cortical areas involved in motor control (Carel et al. 2000).

In addition, it is possible that a combination of the abovementioned spinal and supraspinal mechanisms contributed to an increase of excitability of the nervous system, consequently resulting in an increased tapping rate.

Although the present findings from the passive tapping in studies I-II, do not provide further evidence for differentiation between supraspinal and spinal mechanisms on rate enhancement, it could be argued that sensory feedback is a primary contributor for an increased excitability of the nervous system. However, somatosensory feedback during finger tapping include different inputs from e.g. proprioceptive feedback from muscle spindles and tactile feedback from the cutaneous receptors. Thus, to mimic the freely chosen tapping, a third form of finger tapping was performed in study I, namely air tapping.

4.1.2 Effect of air tapping on rate enhancement

The findings in study I revealed that rate enhancement was also elicited following priming with air tapping, for the participants who previously showed RBRE. The goal of air tapping was to perform a tapping form with a different somatosensory feedback input compared with freely chosen tapping, by omitting the tactile feedback from the impact on the fingertip when tapping on to the force transducer. The present finding of rate enhancement following air tapping indicate that intensive tactile feedback is not necessary to elicit rate enhancement. In continuation hereof, it could be speculated that the contribution of afferent feedback from proprioceptors is of essential importance. Thus, the findings in study I indicate that rate enhancement was regulated independently of the pattern of somatosensory feedback to the motor cortex. This was further underlined by a supportive experiment in study I, where a qualitative analysis of SEP responses showed various patterns of somatosensory feedback between all three tapping forms (i.e. freely chosen, passive and air tapping), see **Figure 14**.

4.1.3 Effect of tapping duration on rate enhancement

Study II further showed that rate enhancement was elicited when various durations of priming in the form of freely chosen and passive tapping was applied. Thus, rate enhancement was elicited following priming with tapping durations of 20, 60 and 120 s, see **Figure 9**. For study II, it was hypothesized that a dose-response relationship between the duration of priming and the magnitude of rate enhancement would be demonstrated. Conversely, there was no difference between the durations of priming and between groups. However, the present findings suggest that individuals susceptible to RBRE merely require 20 s and perhaps even less time of priming to elicit rate enhancement. The finding was in contrast to what was expected. Although the present body of literature, to the best of my knowledge, investigating the effect of time in relation to nervous system excitability is sparse, a few empirical studies could be considered. Thus, animal studies in the sea slug *Aplysia* have previously reported that a priming period of 30 s of electrical stimulation of a CPG regulating the cycle rate of the feeding program, results in a short-term synaptic enhancement during which there is an increase in the cycle rate of the rhythmic ingestion motor program (Sánchez & Kirk 2000, Sánchez & Kirk 2002). In extension, the findings of Sánchez and Kirk (2000, 2002) indicate that upregulation of the CPG itself, contribute to an increase in cycle rate. In addition, it has been reported that increased supraspinal excitability is present prior to rhythmic arm movement compared with rest, however spinal motoneurone excitability is unchanged (Power & Copithorne 2013). This finding was suggested to reflect that supraspinal strategies are used to prime the motor system before the initiation of the movement, after which spinal CPG's assume the control for the regulation of rhythmic movement. Derived from this suggestion, it seems conceivable that a contribution from supraspinal and spinal mechanisms for the regulation of rhythmic movement can occur separately in humans. Thus, it further seems plausible that elicitation of rate enhancement could be the result of an increased excitation of the nervous system due to a combination of spinal and supraspinal mechanisms.

4.1.4 Comparison of RBRE to other examples of priming

Although the findings in studies I and II do not provide direct measurements of the neurophysiological mechanisms regulating RBRE, the phenomenon could be likened to examples of priming. A related priming example could possibly be movement-based priming (Stoykov & Madhavan 2015, Stoykov et al. 2017, Jordan & Stinear 2018). The example of movement-based priming is being, in line with other forms of priming, used in restorative therapy in order to improve function by targeting underlying neural mechanisms (Pomeroy et al. 2011, Stoykov et al. 2017). Movement-based priming

has been described as any type of repetitive or continuous movement, which is performed to enhance the effect of concomitant therapy (Stoykov & Madhavan 2015), and has been assessed by measurements of e.g. hand grip strength (Stinear et al. 2008). It has been reported that movement-based priming can be induced by unilateral repetitive movements in the form of both active and passive movements (Stoykov & Madhavan 2015). Furthermore, movement-based priming has been considered to be caused by changes in the central nervous system excitability, through the release of neurochemicals that induces neuroplastic effects which may enhance the effect of subsequent movement (Stoykov et al. 2017). Thus, it could be speculated that RBRE could be considered as a related type of movement-based priming. However, it must be noted that the neural mechanisms involved in movement-priming has been associated with a decrease in cortical inhibition (Stoykov & Madhavan 2015, Stoykov et al. 2017). Therefore, relating the phenomenon of RBRE to movement-priming, it could be that an increase in tapping rate is the result of a decreased tonic inhibition (Benjamin et al. 2010). Thus, Benjamin et al. (2010) argued that 'a general function for tonic inhibition is to prevent unnecessary non-goal directed activity that would be energetically expensive', and further that motor programs might be a specific target for tonic inhibition because many motor programs involve CPG's that are often spontaneously active and therefore need to be actively suppressed for energy conservation.

Another related example of priming could be a mechanism termed repetition priming (Cropper et al. 2014, Siniscalchi et al. 2016, Cropper et al. 2017). Repetition priming has been defined as 'a progressive improvement in performance when behaviour is repeated' and can be measured as increases in e.g. speed, accuracy and response amplitude (Cropper et al. 2014). In addition, it has been argued that through repetitive input activation, effects of neuromodulators become cumulative that leads to a progressive alteration in motor neuron activity (Cropper et al. 2014). The effects of repetition priming persists due to the cumulative effect of neuromodulators before the effects dissipate with time (Cropper et al. 2014). Repetition priming has been described in the feeding program in *Aplysia*, where changes in the excitability of the spinal networks is reconfigured through intrinsic neuromodulators caused by repetitive movements (Cropper et al. 2017). Although the findings was reported in *Aplysia*, the reported mechanisms underlying repetition priming was suggested to be similar in human behaviour when performing episodic repetitive movements (Cropper et al. 2017).

4.2 Effect of rate enhancement on muscle activation

In study I, muscle activation was measured during all three forms of finger tapping. The reasons to include measurements of muscle activation were two-fold. First, to verify that the passive tapping was performed in an intended manner. Second, the amount of muscle activation has been suggested to reflect, to a certain degree, supraspinal descending drive (Löscher et al. 1996, Carpentier et al. 2001, Arabadzhiev et al. 2010), thus changes in muscle activation could intuitively be expected as a consequence of an increase in tapping rate.

With regard to the abovementioned first argument, the amount of muscle activation during the passive tapping was significantly lower compared with the freely chosen tapping, see **Figure 12**. This finding confirmed that the passive tapping was performed in an intended manner. However, for completeness it should be noted that a small amount of muscle activation was measured for both the EDC and FDS muscles during the passive tapping. For comparison, other studies investigating passive finger movement have previously reported no sEMG activity (Onishi et al. 2013, Nakagawa et al. 2017, Sasaki, R. et al. 2017). These differences could possibly be explained by differences in sEMG recording procedure and finger movement tasks. Thus, the studies from Nakagawa et al. (2017) and Sasaki et al. (2017) applied passive finger movement in the horizontal direction, whereas the passive finger movement in the present project was performed vertically. The EDC and FDS muscles are primary muscles responsible for flexion and extension of the index finger, however they are also responsible for contraction of the middle, ring and little fingers. Thus, unintended movement of the middle, ring or little fingers could influence the sEMG recordings (Arunachalam et al. 2005).

With regard to the abovementioned second argument, the amount of muscle activation between the first and second tapping bout performed at freely chosen rate was not statistically different. This finding indicated that the increased tapping rate in the second bout occurred without enhanced descending drive. Instead, it could be that the rate enhancement occurred non-volitional, due to a net excitation of the spinal CPG (Frigon 2017). This could result in a modified output from the CPG, but without changed central neural drive and thus gross sEMG activity, see **Figure 17** (panel B).

As a result of the abovementioned finding, a supportive experiment was performed in study I was performed to test the sensitivity of the sEMG recordings. The supportive experiment showed that a significant difference in the amount of muscle activation of the EDC muscle could be detected when tapping was performed volitionally at pre-set tapping rates, corresponding to the average tapping rates measured in the first and second tapping bout on a group level, in the main experiment in study I. This finding confirmed that the method of sEMG recordings was sufficiently sensitive to detect a

possible difference in muscle activation, that was of a relevant magnitude for the present measurements. Furthermore, the finding indicated that during volitional pre-set tapping, a larger amount of supraspinal descending drive (Löscher et al. 1996, Carpentier et al. 2001, Arabadzhiev et al. 2010) was present compared with the freely chosen tapping, further underlining the possibility of an increased excitation of the spinal CPG during the freely chosen tapping, see **Figure 17** (panel C). The finding, that sEMG activity is increased when pre-set tapping is increased, is in line with a previous reporting (Schnoz et al. 2000).

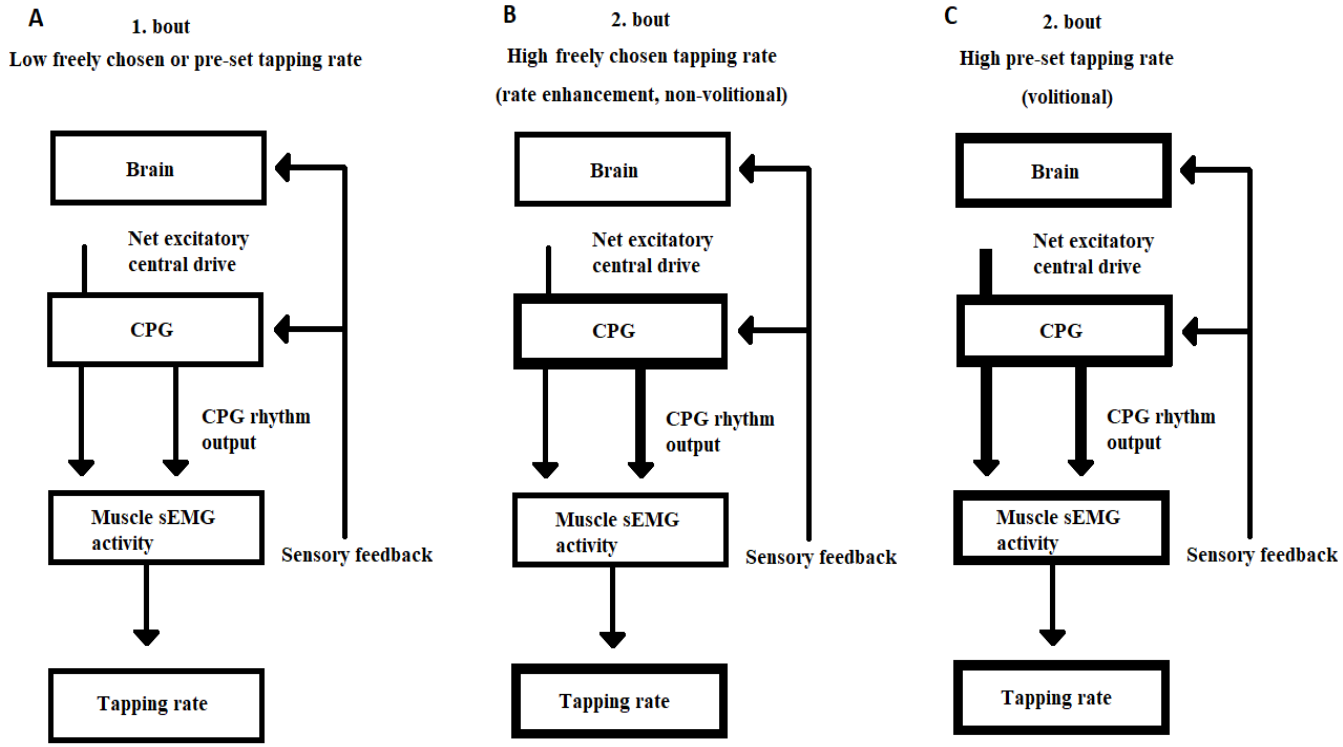

Figure 17. Overview of possible scenarios of neural effects on muscle activation in different tapping conditions. Panel A) represents low freely chosen or low pre-set tapping rate during an initial tapping bout. Panel B) represents increased freely chosen tapping rate during a second tapping bout. Panel C) represents volitional pre-set at high tapping rate as performed in Experiment 2 in study I.

4.3 Effect of rate enhancement on tapping force

In study I, the tapping force decreased during rate enhancement for the freely chosen and passive tapping. This finding was replicated in study II when 180 s of priming was applied for both freely chosen and passive tapping. The results were in contrast to a previous finding, where tapping force was unaffected by rate enhancement following 180 s of freely chosen tapping (Mora-Jensen et al.

2017). The reason for the discrepancy could possibly be explained by differences in study designs, as Mora-Jensen et al. (2017) did not select individuals who showed RBRE for further analysis as done in the present project. On the contrary, Mora-Jensen et al. (2017) investigated the effects of tapping force and vertical displacement in all participants, although 33% of the participants did not show rate enhancement. However, as development of force and timing is highly intertwined (Sternad et al. 2000), concurrent changes in tapping force and tapping rate could be expected. Thus, Sternad et al. (2000) argued that to produce a given movement amplitude at changing movement times, it is necessary to scale the accelerating or decelerating force impulses. Hence, to produce a movement with more force, the central nervous system must either recruit more motor units, implement a change in firing frequency, or a combination of both (Sternad et al. 2000).

In study II, the tapping force was unaffected following 20, 60, or 120 s of priming was applied for both freely chosen and passive tapping. These findings were unexpected and the divergence from the 180 s durations of priming were not of obvious character. However, as there was a main effect of session on tapping force, it could be that the discrepancy was due to type II errors. Thus, test sessions involving 20 and 60 s of tapping showed tendencies towards a reduction on tapping force, whereas the test session involving 120 s of tapping was not different.

4.4 Effect of rate enhancement on vertical displacement of the fingertip

In study I, the vertical displacement of the index fingertip decreased during rate enhancement for the freely chosen and passive tapping. This finding was in line with a previously reported reduction (Mora-Jensen et al. 2017). However, this finding was not replicated in study II, where no changes in vertical displacement was reported following either freely chosen or passive or when taking the duration of priming into consideration. Intuitively, it could be expected that the vertical displacement of the index fingertip would be reduced when the tapping rate is increased, as a consequence of a shorter duration between taps that would likely entail a lower amplitude of finger displacement. Also, a reduced displacement with increased movement rate has previously been reported during cyclic finger movements (Haken et al. 1985). However, the reasons for this discrepancy between studies I and II is not obvious. A possible explanation could be the involvement of different participants between study I and II.

4.5 Responders and non-responders of RBRE

In studies I and II, the amount of participants who did not show RBRE were approximately 36% and 28%, respectively. This was comparable to a previous reporting of 33% (Mora-Jensen et al. 2017). It remains unclear why some participants do not show the phenomena of RBRE. Possible explanations could include that the participant was already in a rate enhanced state, that the participant was not physiologically predisposed to RBRE, or that random error played a role. However, in an attempt to describe characteristics and elucidate possible explanations, motor variability between responders and non-responders of RBRE was investigated in study III. For this, linear (SD and CV) and nonlinear (SaEn) metrics of motor variability applied to kinematic and kinetic time series, were investigated in responders and non-responders of RBRE in study I and II.

A central aspect of motor control is motor variability, which is an intrinsic feature in all biological systems (Stergiou & Decker 2011, Komar et al. 2015). A framework to interpret motor variability is from a dynamic systems theory perspective, where biological systems are presumed to self-organize according to biomechanical, morphological, and environmental restraints to find a steady and balanced solution for producing a given movement (Stergiou et al. 2006, Stergiou & Decker 2011). Thus, it has been proposed that motor variability can be seen as a reflection of the nervous systems' ability to utilize available degrees of freedom of the motor system, which has been described as the ability to take benefit or the redundancy or abundancy of the motor system (Bernstein 1967, Latash & Anson 2006). Moreover, in the framework of abundancy or redundancy, then the central nervous system is being confronted with a choice of how to perform the required motor task (Latash & Anson 2006). Accordingly, variations in motor control strategies can be a reflection of neural adaptability and flexibility towards performing the motor task in an appropriate and optimized manner (Faisal et al. 2008, Stergiou & Decker 2011). Thus, from a dynamic systems perspective, a decrease in magnitude of variability (SD and CV) may indicate that a given movement (i.e. finger tapping) has reorganized towards a more steady state (Stergiou & Decker 2011), whereas it has been suggested that an increase in the structure of variability (SaEn) is generally observed in relation to more experience (Madeleine 2010).

In study III, it was revealed that responders and non-responders of RBRE demonstrated differences in motor variability. It was found that the SD and CV mostly did not differ between responders and non-responders, although a reduction in the SD of vertical displacement was observed for both groups in bout 2 compared to bout 1. More interestingly, the responders had an increase in the nonlinear metric SaEn of vertical displacement from bout 1 to bout 2 compared with the non-

responders. Furthermore, a concomitant increase in the SaEn of vertical force was found for the responders.

Relating the present findings to motor variability in the framework of abundancy or redundancy, it could be argued that the increase in SaEn of vertical displacement from bout 1 to bout 2 for the responders compared with the non-responders, could be a reflection of responders displaying greater ability to utilize available degrees of freedom as opposed to the non-responders (Van Emmerik & Van Wegen 2002). In continuation, it could be proposed that the finding that responders performed finger tapping with a higher complexity in the structure of vertical force and displacement in bout 2 as compared to bout 1, could possibly be a reflection of an increased exploration and thus a greater dynamic control of the motor pattern of the finger during finger tapping.

In extension of the findings that the responders had higher SaEn values of vertical displacement and force in bout 2 compared with bout 1, the proposed neurophysiological mechanisms of increased excitability in the nervous system for the regulation of rate enhancement, could be related to the loss of complexity hypothesis (Vaillancourt & Newell 2002). Briefly, it has been proposed that the complexity of a dynamic system could be a reflection of the underlying structural components (i.e. CPGs and/or supraspinal centres) and the functional coupling (i.e. synaptic efficacy) between the components, see **Figure 18**. Thus, considering SaEn as a reflection of complexity, it could be speculated that the suggested increase of nervous system excitability for the responders responsible for the elicitation of rate enhancement, could be a reflection of an increased dynamic functional coupling between the structural components.

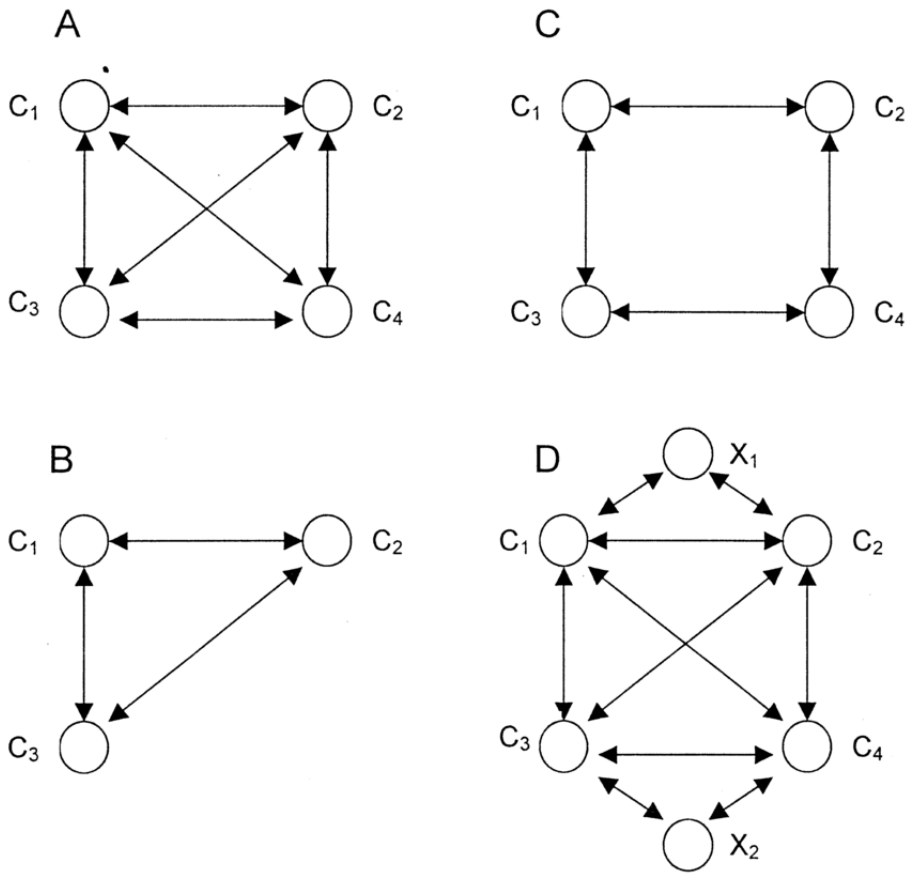

Figure 18. Schematic illustration of the loss of complexity hypothesis. The circles represent structural components. The arrows represent functional coupling between the structural components. **A**, a representation of structural components and functional coupling between the components of the system. **B**, represents the loss of complexity by the loss of a structural component from the system, which can be related to age and/or disease. **C**, a reduction in the number of arrows represents an alteration in the functional coupling between structural components, which also can be related to age and/or disease. **D**, represents an increase in the number of structural components of the system. Adapted with permission from Vaillancourt & Newell (2002).

For completeness, it must be noted that other interpretations of motor variability has been proposed. Accordingly, it has also been argued that motor variability can be interpreted in relation to effects of practice (Bernstein 1967, Van Emmerik & Van Wegen 2002). Thus, it has been argued that effects of practice can be observed and identified across different domains at different time scales, with observable changes in movement patterns within minutes (Newell & Vaillancourt 2001, Madeleine 2010). Relating the present findings to motor variability in the framework of effects of practice, it could be argued that the performed tapping bouts may well represent a period of practice

and the rest period a consolidation phase (Karni & Sagi 1993). In continuation hereof, it could be speculated that the non-responders did not exhibit RBRE as a result of either a too short tapping period, a too short period of consolidation of motor strategies, or a combination of both. On the contrary, it could be that the responders were able to process the information provided to the motor system within the first tapping bout, thus displaying an ability to develop their motor repertoire. This notion is further supported by the finding that the SaEn of vertical force and displacement increased between bouts, and that the SaEn of vertical force increased with time for the responders whereas it remained unchanged for non-responders, see **Figure 16**. Thus, it could be argued that the responders had a transition in the level of practice, which was characterized by a release of degrees of freedom and accordingly an increased adaptability of the motor behaviour. Therefore, it is possible that the sequence of initial exploration, identification of a solution and subsequent capability to release degrees of freedom to adapt to the dynamics a motor task (Harbourne & Stergiou 2003), seems relevant to the findings of motor variability in responders of RBRE.

4.6 Comparison of rate enhancement in finger tapping to other rhythmic movements

For the present project, finger tapping was considered to reflect a CPG-mediated movement (Hansen & Ohnstad 2008, Shima et al. 2011). Other types of rhythmic movements that can be compared to finger tapping include examples such as walking and pedalling (Zehr & Duysens 2004, Stang et al. 2016, Minassian et al. 2017). Thus, an interesting question could be whether a similar effect of rate enhancement could be found in these types of rhythmic movement. Although this question has not been investigated in the present project, some considerations could be of relevance.

First, it is relevant to consider the differences in the segments that are involved in the rhythmic movements. Thus, finger tapping as performed in the present project, is performed unilaterally by a small segment of the arm, whereas both walking and pedalling involves bilateral movement of both legs. Therefore, it is conceivable that the descending and the sensory input during finger tapping is different from both walking and pedalling.

Second, it is relevant to consider the involvement of the legs performed during daily life activities compared to the unilateral flexion/extension motion of finger tapping. Although tapping like movements can be involved in e.g. computer keyboard texting (Dennerlein et al. 1998, Kim et al. 2014) or mobile phone use (Olwal et al. 2008), the involvement of the legs to perform rhythmic movements must be presumed to be of greater degree. In extension hereof, it could be speculated that due to the greater involvement of the legs, it is possible that a rate enhanced state is present constantly.

Third, it should also be considered that rhythmic movement of the lower and upper extremities have supposedly changed from an evolutionary perspective. Thus, the locomotion performed with the lower extremities is an evolutionary preferred form of rhythmic movement, which have been reported to be highly optimised with regard to movement economy (Martin et al. 2000, McNeill 2002). In contrast, the use of the upper extremities in humans have evolved and are highly involved in discrete movements, such as reaching and grasping (Schaal et al. 2004). Therefore, it is possible that the human neural control of the upper and lower extremities is different (Zehr et al. 2016, Frigon 2017).

To summarize the three above-mentioned considerations, it is likely that the present findings of rate enhancement found in finger tapping cannot readily be generalized to other rhythmic movements, such as e.g. walking and pedalling. However, the present findings provide further insights to the underlying mechanisms which could be involved in the control and regulation of rhythmic movements in general.

4.7 Methodological considerations

Some methodological considerations of the present thesis can be discussed. It could be argued that the use of only a single measurement of the freely chosen tapping rate from the first to the second bout is insufficient to select individuals for further participation and to perform statistical analyses. A common practice in science is to perform consecutive measurement and derive a mean. However, for the present project it could be argued that the nature of RBRE makes this task very time-consuming, as it has been reported that a two week washout period is required to ensure that the freely chosen tapping rate is reset (Hansen & Ohnstad 2008). In addition, when studies involving measurements of the freely chosen pedalling rate are performed, it is also common to merely perform a single measurement for reference (or baseline) (Bessot et al. 2008, Leirdal & Ettema 2011, Hartley & Cheung 2013). Moreover, Hansen et al. (2015) reported that the between-day reliability of the freely chosen tapping rate is high (ICC = 0.94). This result was further supported by a similar between-day reliability test-retest in study II, which showed a high $ICC_{(3,1)}$ of 0.85.

The purpose of the present project was to further investigate the phenomenon of RBRE. The phenomenon was reported (Hansen et al. 2015) and subsequently replicated (Mora-Jensen et al. 2017). In the present studies, the phenomenon was replicated once again and selected participants to only study those who showed the phenomenon. The procedure of merely studying individuals who show a phenomenon, or respond to a test, and disregard other individuals is common practice within the field of motor control (Hall et al. 1999, Motl et al. 2004, Vangsgaard et al. 2014, Chen et al. 2015).

4.8 Limitations

Some limitations of the present thesis should be considered. The present thesis has focused on voluntary stereotyped rhythmic movement's behaviour during repeated bouts of finger tapping. It is acknowledged that the primary variables used to interpret the present findings consisted of indirect measurements of force and kinematic recordings, and that evaluation of neuromuscular and morphological adaptation in the form of muscle activation and SEP recordings was only applied in study I. In other words, other techniques, such as e.g. functional magnetic resonance imaging (fMRI) (Buijink et al. 2015, Cleland & Schindler-Ivens 2018), transcranial magnetic stimulation (TMS) (Carroll et al. 2006, Solopova et al. 2014), or magnetic resonance spectroscopy (MRS) (Wyss et al. 2016, Stanley & Raz 2018) are required to elucidate the potential neural mechanisms that may be important for the observed alterations in voluntary rhythmic movement. Still, we are limited for investigating and describing the interrelationship between supraspinal, spinal, and sensory input during voluntary rhythmic movement in humans. Therefore, behavioural studies as performed in the present thesis are needed for advancing the understanding of the movement behaviour during human voluntary rhythmic movements.

Another limitation of the present thesis, is that study II did not include sEMG recordings of possible voluntary muscle activation. Thus, the amount of voluntary muscle activation during the passive tapping task was not quantified. The choice not to include measurements of muscle activation, was primarily due to the extensive time to perform the tapping sessions with the required amount of participants. Although a more comprehensive familiarization period was provided compared with study I, and the fact that an objective evaluation of each tapping bout was performed, it cannot be excluded that some muscle activation was present during the passive tapping bout in study II.

5 CONCLUSIONS

The overall aim of this Ph.D. thesis was to increase our understanding of voluntary stereotyped rhythmic movements, with a main purpose to investigate and further elucidate the phenomenon of RBRE during the task of finger tapping. Thus, the present project demonstrated that RBRE was elicited by various types of finger tapping, including freely chosen, passive, and air tapping. The elicitation of RBRE following passive tapping could indicate that sensory feedback in itself is sufficient to elicit RBRE. Furthermore, it was demonstrated that rate enhancement was elicited independently of the duration of the first tapping bout, using a range of tapping durations from 20 s to 180 s. The findings indicate that a duration of as little as 20 s is sufficient to elicit rate enhancement, in the form of both freely chosen and passive tapping. Supportive experiments further demonstrated that RBRE occurred in the absence of an increase in muscle activation, whereas it was also demonstrated that rate enhancement occurred regardless of different pattern of prior sensory feedback to the motor cortex. Moreover, differences in characteristics of motor variability between individuals who showed or did not show RBRE were found. Thus, it was demonstrated that the SaEn of vertical displacement was higher for the responders than non-responders. In addition, that the SaEn of vertical force and displacement was higher in the second bout compared to the first bout for the responders. The results could be interpreted to reflect differences in the dynamics of finger tapping between responders and non-responders. Moreover, the findings could indicate a greater adaptability to the motor task of finger tapping for the responders compared with the non-responders.

In summary, the present findings provide new insights into the motor control of human voluntary stereotyped rhythmic movement during finger tapping. Although the underlying neural mechanisms governing RBRE and rate enhancement has not been uncovered

6 PERSPECTIVES

To further advance our understanding of RBRE and to elucidate the underlying neural mechanisms potentially involved in RBRE, other techniques, such as e.g. MRS, are required. Based on the findings in the present thesis, it was proposed that RBRE could be the result of an increased excitability of the nervous system, caused by the release of neuromodulators. Thus, it is possible that the use of MRS could be applied to elucidate whether the phenomenon of RBRE occurs concurrent to changes in neurotransmitter levels (Wyss et al. 2016, Stanley & Raz 2018). In addition, the use of MRS could potentially be applied to both spinal and cortical measurements of changes in neurotransmitter levels (Wyss et al. 2016, Stanley & Raz 2018). For this experiment, it is conceivable that measuring specific neurotransmitter levels prior to a 3-min tapping bout and then again after the tapping bout could reveal whether changes in neurotransmitter levels occur concurrent to a change in tapping rate. However, it must be noted that the application of MRS is methodologically challenged. First, it is a requisite to be aware of which specific neurotransmitter to investigate beforehand. As our present knowledge on which potential neurotransmitter could be involved in RBRE is inconclusive, it is only possible to speculate which neurotransmitter would be relevant to investigate. However, a possible starting point could be serotonin or dopamine, as these have been proposed to be involved in the activation of the spinal circuitry and cortical areas (Miles & Sillar 2011, Wei et al. 2014, Sharples et al. 2014, Perrier, Cotel 2015, Hofstoetter et al. 2017). Second, MRS is challenged by localization which imply it is only possible to focus on a preselect area, hence limiting the possibility to study the entire region of interest (i.e. spinal cord or the brain) (Wyss et al. 2016). Third, although MRS has been applied extensively to investigate the brain, applying MRS to the spinal cord is further challenged by signal quality and resolution of the method, due to both the deep location inside the body (close application of coils is not possible) and the elongated anatomy of the spinal cord (small area to obtain enough signals) (Wyss et al. 2016). Thus, with MRS it will still be a challenge to examine and comprehend the potential role of neurotransmitters involved in RBRE.

In the present project, only asymptomatic individuals were included. The results could possibly been different in a population with e.g. neuromuscular diseases or disorders. Thus, it could be interesting to perform similar studies in patients with Parkinson's disease (PD). PD is defined by a progressive loss of dopaminergic cells in the substantia nigra pars compacta and a consequent loss of striatal dopamine (part of the basal ganglia, see **Figure 3**) (Maetzler & Hausdorff 2012). Although PD is primarily associated to impairment of supraspinal regions, it has also been proposed that impaired CPG access by central and sensory activation is present in PD patients (Selionov et al. 2013,

Ivanenko et al. 2017). This is further in line with the proposal that dopamine is involved in the activation of the spinal and cortical circuitry (Miles & Sillar 2011, Hofstoetter et al. 2017). Bradykinesia (slowness of initialising voluntary movement) is a hallmark of PD (Adams 2017), and assessment of dexterity (skill in performing tasks with the hands) by finger tapping shows slowing, reduced amplitude of movement, and irregular cadence that become more apparent as the patient continues the movement (Nutt & Wooten 2005). Further, fine movements are affected more than large movements and repetitive movements also suffer (Nutt & Wooten 2005, Adams 2017). Thus, the contrasting observations on bradykinesia in PD patients and elicitation of RBRE in asymptomatic individuals could potentially be an indicator of a characteristic of a motor symptom for detection of early neuromuscular disease. Thus, it has been argued that identifying tests of motor symptoms is highly relevant for detection of early PD (Maetzler & Hausdorff 2012, Mantri et al. 2018), as PD can be difficult to detect and is commonly misdiagnosed or the diagnosis is missed completely (Pahwa & Lyons 2010, Adams 2017). Furthermore, a clinical diagnosis of PD can only be performed when the first motor symptoms occur, at which time a non-reversible neurological impairment has occurred (Berg 2008, Pagan 2012, Miller & O'Callaghan 2015). Thus, it has been argued that identification of motor control tests for early diagnosis of PD is a requisite for better treatment (Maetzler & Hausdorff 2012, Pagan 2012, Mantri et al. 2018).

7 THESIS AT A GLANCE

Title of study:	Primary aim	Method	Main finding
Study I			
Repeated bout rate enhancement is elicited by various forms of finger tapping	To investigate whether repeated bout rate enhancement would be elicited in the absence of descending drive	Measuring the freely chosen tapping rate along concomitant kinetic, kinematic and sEMG recordings during finger tapping, following priming including freely chosen, passive, and air tapping	RBRE was elicited by freely chosen, passive, and air tapping. The elicitation RBRE following passive tapping could indicate that sensory feedback in itself is sufficient to elicit RBRE
Study II			
Effect of tapping bout duration during active and passive finger tapping on elicitation of rate enhancement	To investigate whether there is a dose-response relationship between the duration of priming and the magnitude of rate enhancement	Measuring the freely chosen tapping rate along concomitant kinetic and kinematic recordings during finger tapping, following priming including freely chosen and passive tapping	Rate enhancement was elicited independently of the duration of the first tapping bout, using a range of tapping durations from 20 s to 180 s. The findings indicate that a duration of as little as 20 s is sufficient to elicit rate enhancement, in the form of both freely chosen and passive tapping
Study III			
Motor variability in elicited repeated bout rate enhancement is associated with higher sample entropy	To investigate motor variability in responders and non-responders of repeated bout rate enhancement	Linear (SD and CV) and non-linear (SaEn) metrics were extracted from kinetic and kinematic time series of freely chosen finger tapping	Differences in characteristics of motor variability between individuals who showed or did not RBRE was demonstrated. A common observation was that SaEn differed between the groups

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9 APPENDICES

I Emanuelsen, A., Voigt, M., Madeleine, P., Kjær, P., Dam, S., Koefoed, N., Hansen, E. A. Repeated bout rate enhancement is elicited by various forms of finger tapping, Frontiers in Neuroscience (2018), 12:526.

II Emanuelsen, A., Voigt, M., Madeleine, P., Hansen, E. A. Effect of tapping bout duration during active and passive finger tapping on elicitation of repeated bout rate enhancement, submitted.

III Emanuelsen, A., Madeleine, P., Voigt, M., Hansen, E. A. Motor variability in elicited repeated bout rate enhancement is associated with higher sample entropy, Human Movement Science (2019), 68:102520.

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