Moving in time: Neurons, Clocks, and Rhythmic Movements

Alistair Neil Vardy

VRIJE UNIVERSITEIT

Moving In Time:
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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Bewegingswetenschappen
op woensdag 8 december 2010 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Alistair Neil Vardy

geboren te Bangor, Verenigd Koninkrijk

promotor: prof.dr. P.J. Beek
copromotor: dr. A. Daffertshofer

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CHAPTER I

INTRODUCTION

I.1 SETTING THE STAGE

"I said a hip hop the hippie the hippie
to the hip hip hop, a you don't stop the rock it
to the bang bang boogie say up jumped the boogie
to the rhythm of the boogie, the beat"

Most readers will undoubtedly be tapping their fingers or bobbing their heads by now as they recall the bass line of this song (Rapper's delight) by The Sugarhill Gang (Shugar Hill Records, 1979). I have chosen this first verse to illustrate how important rhythm is to people, and how even a short verse invokes rhythm in the mind. All throughout history, people have produced rhythms by means of music and dance. This thesis, however, does not concern music or dance, but investigates how it is that we are able to produce rhythmic movements.

Scientific research into neural control of rhythmic movements dates back to at least the late 19^{th} century, when Stevens (1886) investigated the timing of finger tapping. This seemingly trivial exercise stimulated a wealth of research into the control of rhythmic movements and motor timing in particular and to this day remains a popular experimental task. In contrast to the 19^{th} century, we can currently track fingers in 3-dimensional space with millisecond and millimeter precision. We can also record nervous activity going to the muscle (Mano et al., 2006) or record muscle activity from the skin (Vannozzi et al., 2010) offering insight into the signals produced by the brain to make the fingers tap. In fact, analyses are no longer restricted to nervous activities in muscles as we are even able to 'look inside' the brain and record some of its activity with great detail using a wide array of measurement techniques. Despite all these advances, it remains unclear how we keep time when performing rhythmic movements. A crucial question for a conceptual understanding

of how the system 'human being' is able to time and perform rhythmic movements with great precision, is whether some sort of clock exists in the system and, if so, where is it located? In fact, when separating the system 'human being' into its large-scale components brain, muscles, and limbs, one must also uncover how these parts relate to each other to understand what role a clock can play and which components of the system can influence this clock and/or are influenced by it. For example, if we dangle our leg, it will move back and forth at a certain frequency and will keep on doing so with the sporadic burst of activity from participating muscles, e.g., the quadriceps. This is much like a swing that keeps its motion with an occasional push (Post et al., 2007). Occasional pushes suffice to keep the swing or the leg going because of its substantial inertia in the context of gravitation. This is not the case for finger tapping. Our fingers are much lighter than our legs, and the occasional muscle activity is not enough to maintain a (smooth) oscillation. Continuous finger motions require almost permanent and well-coordinated activity from the participating muscles. Coordination of muscle activity demands well-dosed, accurate control that, most probably, stems from the central nervous system.

This line of thought triggers the question whether the brain does in fact need to 'know' all structural properties of the finger and, if so, whether it needs to permanently monitor the finger's dynamical state?[1] In contrast, for the brain it might be sufficient to recognize that it is a finger that needs to be moved, information which merely provides boundary conditions for the controller residing in the central nervous system. We are perfectly able to get into a car and make it swerve from side to side at a wide range of frequencies. This can be done even by a child with no driving experience in real life or behind a game computer. The brain does not need to know the intricacies of the power steering and mechanics of the car.

If a clock is indeed present, is it an independent entity that dictates the actions of the body, or is it an integrated part of the complete system and thereby influenced by the actions and state of the body? The answer to this question is complicated by the lack of a clear definition of the clock. Many units in the brain work together during the production of rhythmic movements and we cannot just go ahead and insert electrodes in the brain. Even if we could, we would probably still not be able to detect a clock, as similar oscillatory activity will be measured in large portions of the brain. The path I have chosen here is to assimilate the results of timer models and experiments to investigate the existence,

[1] The finger's *state* refers to its physical properties like position and velocity.

uniqueness, and stability of the clock that appears to be involved in the timing of rhythmic movements.

I.2 MODELING THE CLOCK

The movements discussed in this thesis are rhythmic, voluntary and self-sustained. Such movements require a sense of timing. When analyzing movement kinematics, one can deduce performance and investigate if someone has 'better' timing than someone else. The aim of rhythmic movement lies not within the clock, but in the action that is required; the beat of a drum, hammering a nail, or tapping one's finger during a boring experiment, and thus it is the behavior that is timed. The brain does not directly move the finger, but rather sends commands to the muscles which in turn produce movement. This muscle driving motor output forms a separate part of the timing of rhythmic movements. By assessing movement kinematics, we can determine movement variability and timing error. These measures are the key ingredients of timer models. Timer models mostly incorporate a clock which is used to keep time. These models can be used to investigate the existence of a clock.

Models of behavior based on clocks abound in literature (Delignières et al., 2004; Vorberg and Wing, 1996; Wing and Kristofferson, 1973) and rely on an abstract simplification of the timer. One of the main advantages is that experiments are straightforward and the behavioral results agree highly with model predictions. As the physiological intricacies of the timer cannot be learned from kinematics alone, each model requires a set of assumptions. Timer models restrict themselves to abstract descriptions of the clock where variability of timers and accuracy of performance form the parameters.

A timer model that is at the basis of many models is the Wing-Kristofferson model (Wing and Kristofferson, 1973), which consists only of a clock and a motor delay. The clock generates so-called clock intervals C_i that are independent identically distributed stochastic variables. The stochastic motor delays D_i are also independent identically distributed stochastic variables that, in addition, are independent of the clock intervals. Inter-response intervals (IRIs) can then be defined as the sum of clock intervals and (differences between) motor delays, i.e. $I_i = C_i + D_{i+1} - D_i$. The structure of the Wing-Kristofferson model determines the correlation structure of the IRIs provided variances of the clock and the motor delays are known. In turn, the variances of C_i and D_i can be inferred from the autocorrelation function of the IRIs (see below). To do so, numerous

well-established paradigms are available (Vorberg and Wing, 1996; Wing and Kristofferson, 1973). In my thesis, I particularly capitalized on the so-called synchronization-continuation paradigm, i.e. subjects performed rhythmic movements in synchrony with a metronome and were asked to continue their movements after the metronome had ceased. The resulting behavioral and electrophysiological data, series of IRIs and electromygrams (EMG) and/or magnetoencephalographic (MEG) signals, respectively, were assessed in terms of their autocorrelation and spectral composition.

INFERENCES FROM TIMER MODELS

Behavioral observations of IRIs reveal similar autocorrelation functions with a negative lag-one autocorrelation and zero autocorrelations for higher lags, implying that, on average, short intervals are followed by long intervals. At first glance one might think that an error-correction mechanism ensures that the target pace is kept. However, the Wing-Kristofferson model, using only feed-forward control, predicts the autocorrelation function found in behavioral experiments. Moreover, it also predicts that the timer variance increases with increasing IRI and that the motor delay variance should remain constant. These predictions have been verified experimentally (Vorberg and Wing, 1996).

Are rhythmic movements indeed controlled in a similar fashion? Simple rhythmic movements such as tapping which only require temporal precision and no spatial precision could well be controlled in a feed-forward fashion. If tapping is indeed subject to feedforward control, then any perturbations to the timer transfer directly to behavior. However, it is unclear if we can perturb the clock independently of the behavior. Hence, we arrive at my first research question of this thesis: *is the timer an object that can be manipulated independently of movement? Or, framed conversely, can the timer be manipulated by movement?*

To assess motor timing, different levels in the generating system have to be investigated: the central nervous system or, here more specifically, the cortical activity in the human brain via MEG; the nervous activity in the movement generating muscle, here the surface EMG, and, of course, the finger or, more generally, the accompanying kinematics. This provides at least three ways of gaining insight into properties of the clock and timing in general. The use of kinematics in modeling the clock has already been discussed. In the following section, I will discuss the use of MEG and muscle activity as a means to locate the clock.

I.3 LOCALIZING THE CLOCK

ACTIVITY OF THE MOTOR AREAS

During the production of rhythmic movement, many parts of the brain are known to be involved. Timing is related to (bilateral) activity in the cerebellum and motor areas, the premotor areas, supplementary motor areas, and the basal ganglia (Grahn and Brett, 2007; Grahn and Rowe, 2009; Ivry, 1997; Ivry et al., 1988). Impairment of any of these areas leads to problems in motor execution, planning, and/or timing. The notion of a clock is thus not as trivial as a dedicated, isolated 'device' located somewhere among the numerous neurons in the brain. As an abstract concept, however, this notion has great value.

Many findings on localized, motor-related brain activity are based on functional magnetic resonance imaging (fMRI), although this technique has quite limited temporal resolution, namely that of picked-up metabolic changes that typically alter over several seconds. To investigate motor timing itself, which is supposed to occur at much faster timescales, we must employ a technique that provides a much higher temporal resolution, namely that of rapid nervous activity, i.e. milliseconds. A technique that satisfies this requirement is magnetoencephalography (MEG). Neural activity measurements, in the form of multi-sensor, whole-head MEG, have been used extensively to analyze the timing properties of the motor areas (see e.g. Houweling et al., 2010b). MEG measures magnetic fields in the brain that are caused by dendritic currents along neurons (Hämäläinen et al., 1993). MEG hence reflects (parts of) the information transfer processing within and transfer between neural populations, in particular in the (neo-)cortex. Given a fairly large number of sensors (in the present thesis more than 100), MEG can provide us with a way of targeting the dynamics as well as the origin of neural activity associated with a particular movement, sensory input, or cognitive processes like attention. MEG recordings can be used to address the questions posed earlier regarding motor timing. In general, MEG signals can be used in a variety of ways. Three analyses, which are central to this thesis, will be briefly discussed.

First, as an MEG system consists of a sensor array arranged in a semi-sphere above the subject's head, this geometry can be used to localize sources of neural activity. Physiologically, the brain cannot be described as a limited number of separate sources, but because of the geometry of the neurons in the cortex where the fibers of many neurons lie in bundles parallel to each other, one can model those bundles as dipoles (Hämäläinen et al., 1993).

Unfortunately, there is a huge number of these dipoles. Moreover, most of these dipoles show activity regardless of the state of the brain. By comparing two different states (like inactivity vs. movement) only the task-related dipoles will change their activity, thereby significantly limiting the number of sources to be investigated. By carefully choosing the different states one can hence focus on the activity in specific areas like the motor cortex, the sensory cortex, and the auditory cortex. Sources can be pinpointed using various localization methods, for instance, beamformers which estimate the power at a given volume of the brain. In this thesis the Synthetic Aperture Magnetometry (SAM) beamformer is used. SAM is based on radar localization techniques which have been adapted for MEG purposes (Vrba and Robinson, 2001).

Second, for raw MEG signals as well as activity at the reconstructed sources, the spectral power (and changes thereof) can be determined. When we change our behavior from inactivity to activity, the power spectrum of MEG changes in specific frequency bands. Although the limits of these frequency bands are somewhat flexible in literature, we restrict ourselves to three frequency bands. The alpha band (7-11 Hz) is related to attention, the beta band (13-30 Hz) to movement execution, and the gamma band (40-70 Hz) to movement preparation.[2] Movement is not only accompanied by real-time changes in neural activity, but these changes in neural activity persist after the movements have stopped. Such after-effects are very important as the subjects are at rest which is a very controlled state affording good comparison between conditions.

Third, to uncover the changes during rhythmic movement one may use averaging techniques to eliminate background noise. When subjects perform tasks which are related to an event (e.g. tapping a sensor), signals may be averaged around this event to generate *event-related fields* (ERF). The shape and amplitude of the ERFs can then be used to quantify differences between experimental conditions.

In my thesis I use all of the aforementioned techniques in conjunction. Timing related changes were sought in after-effects and in changes in spectral content of motor ERFs. These techniques can also be used when investigating how neural activity changes when

[2] Like the frequency bands themselves, the interpretation of those bands involves more than the aforementioned relationships. However, given the simple nature of the tasks used in this thesis, we deem this partitioning of the frequencies and the interpretation thereof sufficient.

certain structures that control timing are impaired. Anticipating the more detailed outline of my thesis, this impairment was in the form of Parkinson's disease where the basal ganglia and the connections with the motor areas are affected. When MEG is recorded during the performance of timed rhythmic movements of a single finger, multiple areas are involved. However, the same areas are active when more than one finger moves, and it is not a priori clear which activity belongs to which finger. Moreover, it is not even clear what activity relates to the timer. A critical question one has to ask here is: if there is activity corresponding to more than one finger moving, do we then also have activity related to more than one timer? This issue will be discussed in the next section.

MULTIPLE TIMERS

When we move, we often move multiple limbs together. Rhythmic movements with more than one limb are not produced as the sum of the movement of two separate limbs, but appear to be controlled as a unit. When we produce a rhythm with two fingers, proper coordination is essential. If we hypothesize two timers, one for each finger, there must be some form of communication between them. That the timing of two moving fingers is influenced by the movements themselves was elegantly illustrated in an experiment by Kelso (1984), the outcome of which was subsequently modeled by Haken, Kelso, and Bunz (1985). In the experiment in question, two fingers start off moving up and down in an alternating, anti-phase, fashion. As the tempo is increased, a critical point is reached where the anti-phase coordination shifts abruptly to in-phase coordination. The anti-phase coordination breaks down and is replaced by the more stable in-phase coordination. In fact, the only phase relationships we can produce in a stable way are in- and anti-phase, where in-phase is more stable than anti-phase (unless we specifically train otherwise). This suggests an interaction between two timers that changes as movement speed increases, and the only coordination pattern that prevails is one that could be produced by a single timer, i.e. both timers produce the same rhythm as this coordination requires the least amount of effort in terms of coordination. It would seem that with increasing effort the ability to control the more complex coordination is lost. Note that the in-phase relationship is not the most stable coordination pattern for all rhythmic movements. When we walk and break into a run (corresponding to anti-phase coordination of the legs), for instance, we will never start hopping with two legs because running becomes too difficult (although a kangaroo keeps on hopping under all circumstances).

The notion of multiple timers has been used to model the temporal control of multiple limbs during rhythmic movement surpassing the performance of models using only one timer (Ivry and Richardson, 2002). If there are indeed multiple timers controlling our limbs, the central nervous system should have a way of coordinating the activity of these timers.

COORDINATION OF MULTIPLE TIMERS

If we conclude that there are indeed multiple timers, then how are they coordinated? We may seek the answer to this question by looking at how the two hemispheres of the brain are connected. Physiologically, the left and right hemispheres are connected by the corpus callosum, a large neural highway of myelinated fibers that convey activity at a very high rate. The relevance of this connection is revealed when we consider the development of infants. When infants move, they commonly move both limbs at the same time and are unable to control their limbs independently of each other. The motor system uses the corpus callosum as a bridge to allow proper control of two moving, bilateral limbs by inhibiting activity of the opposing motor area at specific time intervals during the movement cycle (Daffertshofer et al., 2005). Myelinization of the fibers in the corpus callosum is completed at approximately the age of ten (Duque et al., 2005). Before that age, the unmyelinated fibers in the corpus callosum carry neural impulses 5 to 50 times slower than their myelinated fibers counterparts which conduct neural impulses up to 100 m/s. (Wilmore and Costil, 1999). This implies that the influence of one hemisphere on the other is more effective when the corpus callosum is myelinated.

Mirror movements, or mirror activity,[3] are unimanual movements accompanied by unintentional neural activity or movement of the homologous limb. Their occurrence depends on the task at hand and on task difficulty, where more demanding tasks (in terms of movement speed of produced force) result in more mirror movements (Armatas and Summers, 2001; Armatas et al., 1994; Bodwell et al., 2003; Todor and Lazarus, 1986). Mirror movements arise when the communication between hemispheres is disrupted. The presence of mirror movements supports the notion that unimanual movements should be interpreted as bimanual activity where the output of one effector is suppressed. A mathematical model for this was provided by Daffertshofer, van den Berg, and Beek (1999). Foundational evidence for this model is the ubiquitous experimental finding of bilateral activity in the motor areas during unimanual movements. The occurrence of mirror movements and

[3] For the sake of simplicity, we will refer to both mirror activity and mirror movements as mirror movements.

the phase relationship between the activity of the moving and non-moving hand provide insight into how timers, corresponding to the two fingers, interact. I therefore conclude this part with the second and third research questions of this thesis: *does the interplay between the timers of two fingers have a fixed phase relationship during the production of unimanual movements, or does it exhibit similar properties to those found during bimanual movements? Moreover, can this phase relationship be altered similar to the way bimanual coordination patterns are changed?*

I.4 CHALLENGING THE CLOCK

When we want to know how a car or a television works, we can simply take it apart and look at what the individual parts do. When investigating human movement, things are not that simple. To determine the properties of different 'parts' of the human motor system, we have to perform our measurements while looking at the complete system. As such, the only way to gain insight into separate components is to perturb them somehow. In the following sections I will discuss three types of 'perturbations' that may all serve to gain insight into the afore-listed two overarching research questions on timing that have been posed in the previous sections. The first is a manipulation through experimental design; manipulating a to-be-followed metronome by means of drift. The second refers to the aforementioned involuntary co-activation of homologous muscles, that is, mirror movements in a rhythmic task. The third builds on altered timing in neurodegenerative pathology, here Parkinson's disease, and its interplay with metronome-based cueing.

METRONOME-INDUCED DRIFT

The Wing-Kristofferson model aims to explain the variance found in self-paced tapping by the combined variances in the clock and the motor delay. This model has been found to accurately predict the temporal variation seen in stationary, non-paced tapping. The model also predicts that disturbances in the timer should transfer to the produced movements without hinder. Perturbing the clock however is not easily done due to its abstract nature. The perturbation I have employed is a continuous deterministic change in tapping tempo, a linear drift in the clock interval. The model predicts that removing the drift from the measured sequence of inter-tap intervals should yield a sequence which adheres to the Wing-Kristofferson model, i.e. the autocorrelation function should be negative at lag-one autocorrelation and zero for higher lags. This very simple perturbation has two advantages:

experimentally, it is very easy for subjects to understand and addresses exactly what we interpret as being the clock. In addition, the experiment is easy to run and measurements are accurate. However, whether subjects are able to perform a perfectly linear drift in their clock interval remains to be seen.

MIRROR MOVEMENTS IN RHYTHMIC MOVEMENT

In essence, two types of perturbations were employed when investigating the interplay between two timers during the production of rhythmic unimanual movements. On the one hand, the subjects' motor system was probed to produce mirror movements using a reasonably challenging, rhythmic motor task. This perturbation is instrumental as we are interested in the ability of the motor system to produce mirror movements that have phase relationships comparable to bimanual coordination. As said, the human motor system can produce two phase relationships in a stable fashion: in-phase and anti-phase. On the other hand, subjects were asked to perform coordinated bimanual movement in in- and anti-phase coordination prior to the experimental task that induced the mirror movements in the expectance of certain after-effects. By analyzing the phase relationship of the detected mirror movements, it may be possible to assess the flexibility of the two timers to exhibit phase relationships other than in-phase during unimanual movements.

CUEING IN PARKINSON'S DISEASE

Changing temporal aspects of the clock or the phase relationship between clocks can be done through experiments. Changing the brain itself is impossible on ethical grounds. To gain deeper understanding of the brain we used a 'technique' that has been used for centuries to connect behavioral and physiological problems: pathology. Parkinson's disease (PD) was named after James Parkinson who in 1817 first described this disease in '*An essay on the shaking palsy*'. Later, this disease was related to decrease in dopaminergic neurons in the striatum. PD is now considered a multisystem disorder involving motor and cognitive dysfunction.

PD patients have difficulty performing rhythmic tasks like walking (Morris et al., 1996; Kwakkel et al., 2007). Not only is the production of rhythms disrupted (Harrington et al., 1998), but also the perception of rhythm (Grahn and Brett, 2009), indicating an overall effect of PD on timing. To now state that we can use PD itself as a perturbation for timing

would be similar to using a broken leg to perturb running; it would not add to our understanding of running. However, performance of rhythmic tasks can be restored to a certain degree by providing patients with a rhythm. This is the basis of cueing therapy. In cueing therapy, PD patients are presented with rhythmic cues which can be presented as audible tones, flashes of light, or tactile stimuli. Where PD patients usually suffer from the inability to start walking or the tendency to freeze during walking, the cues alleviate this inability resulting in faster and more stable gait. The improvements are quite remarkable and do not require any form of practice (van Wegen et al., 2006). In PD, the circuits controlling timing are thus not gone, but need a certain type of stimulation to perform complex tasks.

The improvements induced by cueing therapy offer an experimental window into changes in timing in PD. Even during simple tasks there is an underlying change. By analyzing neural activity during the production of rhythmic tasks, we can assess which aspects of this activity are changed in PD. Note that, in this thesis, cueing is used instrumentally; it is not our aim to prove the efficacy of cueing but it is used as a means of investigating neural activity during timing tasks. During cueing, changes occur which improve patients' behavior. It is unclear how these changes come about. MEG can be used to investigate neural activity during cued rhythmic movements, and investigate if changes in neural activity persist beyond the time at which cueing was present, thereby providing long-lasting benefits instead of momentary improvements.

With regard to timing in the context of this particular pathology, I pose the fourth and fifth research questions of this thesis: *are there changes in neural activity that persist beyond the period of rhythmically cued movements into periods of rest? Also, how does neural activity change during cued rhythmic movements, and how does this change depend on the severity of the disease?*

I.5 OUTLINE OF THIS THESIS

In Chapter II, I investigated if the clock can be perturbed without perturbing the movement; if not, this would help to confirm the validity of timer models. To this end, subjects tapped to a metronome with a predictable increase in frequency. According to the Wing-Kristofferson model, this increase in frequency should be mapped one-to-one onto the taps produced by the subjects as only the timer intervals are changed. Removal of the change

in tempo should result in a sequence which is comparable to a sequence with a constant tempo, and thus have a comparable autocorrelation structure.

In Chapter III, I focuses on after-effects of bimanual movements on the phase relationship of unimanual movement and accompanying mirror movements. If the control of unimanual movements involves interhemispheric coordination, then priming the motor system with a certain coordination pattern will persist during the control of mirror movements. By priming the motor system with rhythmic movements involving a specific phase relationships between two fingers, we elicited mirror movements. The analysis of the phase relationships of those mirror movements was used to determine to what extent motor coordination produces after-effects in subsequent unimanual movement, and if the found phase distribution was related to the former.

In Chapters IV and V, I employed PD as a 'perturbation' of the timing circuits. In Chapter IV, I analyzed changes in cortical activity during the performance of rhythmic activity in the presence of cueing. Also, changes in cortical activity as a consequence of rhythmic movement during resting state were examined to identify possible differences in the neural control of timing. These changes in control can then be used to gain insight into the neural underpinnings of cueing therapy. In Chapter V, I discuss slowing of neural oscillation as a result of PD, building upon previous results where this phenomenon has been found during resting state. The primary aim of this study was to investigate this slowing during the production of rhythmic movements. As cued movements improve motor-related problems in PD, it is of great interest to investigate how movement, with or without cueing, alleviates this slowing.

In Chapter VI, the results described in this thesis are integrated and discussed. Also, technical difficulties encountered in the experiments described in this thesis are elaborated upon. In anticipation, I will discuss limitations regarding MEG recordings and their use in studying issues of motor timing. MEG is a valuable asset in neuroscience but has a number of serious limitations. The first is its sensitivity to external noise and movement. In view of this this sensitivity, the experiments were conducted in a highly constrained and reduced environment where subjects have to sit as still as possible. The experimental tasks are thus limited to small movements of the fingers. Second, the signal-to-noise ratio is very poor hampering the detection of single events which is necessary to verify timer models. Finally,

new avenues of research will be proposed to extend this work, but also to overcome some of the above mentioned technical difficulties.

CHAPTER II

TAPPING WITH INTENTIONAL DRIFT

Abstract

When tapping a desired frequency, subjects tend to drift away from this target frequency. This compromises the estimate of the correlation between inter-tap intervals (ITIs) as predicted by the two-level model of Wing and Kristofferson which consists of an internal timer ('clock') and motor delays. Whereas previous studies on the timing of rhythmic tapping attempted to eliminate drift, we compared the production of three constant frequencies (1.5, 2.0, and 2.5 Hz) to the production of tapping sequences with a linearly decreasing inter-tap interval (ITI) (corresponding to an increase in tapping frequency from 1.5 to 2.5 Hz). For all conditions a synchronization-continuation paradigm was used. Tapping forces and electromyograms of the index-finger flexor and extensor were recorded and ITIs were derived yielding interval variability and model parameters, i.e. clock and motor variances. Electromyographic recordings served to study the influence of tapping frequency on the peripheral part of the tap event. The condition with an increasing frequency was more difficult to perform, as evidenced by an increase in deviation from the intended ITIs. In general, tapping frequency affected force level, inter-tap variability, model parameters, and muscle co-activation. Parameters for the condition with a decreasing ITI were comparable to those found in the constant frequency conditions. That is, although tapping with an intentional drift is different from constant tapping and more difficult to perform, the timing properties of both forms of tapping are remarkably similar and described well by the Wing-Kristofferson model.

Adapted from:

A. N. Vardy, A. Daffertshofer, and P. J. Beek, Tapping with intentional drift. *Exp Brain Res*, 192(4):615-625, 2009.

II.1 INTRODUCTION

The search for timing mechanisms underlying the production of repetitive movements has a long tradition dating back as far as the late 19th century (Stevens, 1886). Rhythmic finger tapping has received much interest from researchers of motor control because it provides an expedient window into neural timing. Although many brain areas participate in the timing of motor behavior – including the supplementary motor area (Grahn and Brett, 2007), cerebellum (Del Olmo et al., 2007; Ivry, 1997; Ivry et al., 1988), basal ganglia, thalamus, and motor and sensory cortices (Ivry and Richardson, 2002) – the notion of a single, abstractly defined, neural timer has proven rather successful in accounting for behavioral data.

A case in point is the two-level model proposed by Wing and Kristofferson (1973) – here referred to as the Wing-Kristofferson model – to account for the serial correlations between successive time intervals. The model consists of a clock, defining the duration of the interval between two neural commands, and motor delays, which represent the time it takes for a neural command to reach the end-effector, i.e. the lag at which the tap occurs. The model does not require any assumptions regarding the origin of the clock, only that the timing intervals are independent. Since its inception, the Wing-Kristofferson model has been frequently used to analyze tapping sequences in a so-called synchronization-continuation paradigm, in which subjects first synchronize their tapping to a metronome and then continue the previously indicated rhythm after removal of the metronome (Ivry and Richardson, 2002; Wing and Kristofferson, 1973; Musha et al., 1985; Pressing, 1998; Pressing and Jolley-Rogers, 1997; Vorberg and Wing, 1996). The elegantly simple Wing-Kristofferson model provides an adequate description of various statistical properties of tapping sequences during continuation that can stand up to more elaborate models, which typically place more emphasis on long-term correlations in voluntary tapping (see e.g. Chen et al., 1997; Daffertshofer, 1998; Delignières et al., 2004).

In this study, we examine the generality of the Wing-Kristofferson model by manipulating task difficulty using motor performances with changing tempo. We analyze the temporal properties of inter-tap interval (ITI) sequences in terms of their variance, autocorrelation, and Wing-Kristofferson model parameters, for isochronous and non-isochronous tasks. Pilot studies indicated that a non-isochronous task was more difficult to perform than an isochronous one. Task difficulty affects performance in a number of ways. On a behavioral

level, mental load influences biomechanical properties of rhythmic finger movements (Loehr and Palmer, 2007) and more difficult tasks (tapping a rhythm) display more variability (Doumas and Wing, 2007). Furthermore, cortical areas may be activated differently during simple and difficult tasks. Gerloff et al. (1998) showed that perturbations of the primary motor area using transcranial magnetic stimulation resulted in more performance errors during complex tasks than during simple tasks. Different cortical areas reveal different interactions as a result of task difficulty (Manganotti et al., 1998), and the temporal structure of neural activity is generally influenced by increased mental load (Dhamala et al., 2002).

In isochronous tapping subjects deviate from the fixed target tapping frequency by means of long-term drift (Vorberg and Wing, 1996). This unintentional phenomenon has proven detrimental to the fit of the Wing-Kristofferson model as it may either result in corrections that yield long-term correlations (e.g. Ding et al., 2002; Kaulakys, 1999) or, when monotonic, in non-stationary time series leading to improper estimates of the autocorrelation function and ultimately in a poor model fit. A sharp distinction between long-term properties and non-stationarity is difficult to make since unintentional drift is hard to control experimentally. In practice, many experimenters keep time series as short as possible to minimize the influence of drift.[1] Instead of regarding drift as a confounding factor, however, it may be studied in its own right and explicitly incorporated in the experimental design. By introducing intentional drift, drift may become steady and hence predictable enough to be corrected by linear detrending (Vorberg and Wing, 1996). Such an approach has been used to study synchronization error (Schulze et al., 2005) and subjects' ability to sustain drift during the continuation phase of a synchronization-continuation paradigm (Madison and Merker, 2005). To date, however, intentional drift has not been analyzed against the background of the Wing-Kristofferson model. Here, we apply intentional drift to study temporal properties of tapping a non-constant sequence.

Does intentional drift modify task difficulty and does this mean that the Wing-Kristofferson model fails to describe the behavioral data? An inaccurate description may be caused by the emergence of temporal correlations in the presence of intentional drift. Such correlations may imply that other mechanisms become involved, reflecting the large

[1] More recently, though, efforts have been made to analyze (Madison, 2001) and to model (Collier and Ogden, 2004) unintentional deviations from isochronous tapping.

number of brain areas that are active in neural timing. Indeed, a change in tempo can have profound influences on the temporal properties of motor performance even if the change is constant.[2] In general, tapping a sequence with increasing or decreasing tempo cannot be continued forever, unlike tapping at a constant pace (attentional and energetic limitations aside). Anticipating the up-coming saturation in pace may require additional planning, at least to some degree, making the intentional drift task more difficult, in turn affecting the temporal structure of the sequence preceding saturation. To anticipate, for our subjects (non-musicians), intentional drift sequences did impose an additional burden on performance. However, performance remained adequate so that, after linear detrending, we could analyze temporal properties of intentional drift sequences similar to tapping at a constant pace, that is, in terms of a timer and its autocorrelations. Put differently, the Wing-Kristofferson model remained applicable to tapping with a constant, intentional drift. In addition, we estimated motor delay variability in the Wing-Kristofferson model and its tempo dependence using electromyograms (EMGs) of the finger flexor and extensor muscles. The combination of the flexor and extensor EMG was used to calculate a measure of muscle co-activation, which may influence the motor delay.

II.2 THE WING-KRISTOFFERSON MODEL

The Wing-Kristofferson model is depicted schematically in Figure II.1. In brief, the model supposes that inter-tap intervals (ITIs) arise from clock intervals C_i and motor delays D_i. Both sequences are assumed to be independent in time and independent from each other. Under this assumption, the ITI is defined by $I_i = C_i + D_{i+1} - D_i$. Then, the ITI variability is determined by only two parameters: the clock interval variance σ_C^2 and the motor delay variance σ_D^2. These parameters can, in turn, be estimated using the autocovariance of the ITI sequences at lag zero and one: $\sigma_D^2 = \gamma(1)$ and $\sigma_C^2 = \gamma(0) + 2\gamma(1)$, in which $\gamma(k)$ denotes the ITI autocovariance at lag k. These forms can be combined as

$$-0.5 \leq \left[\frac{\gamma(1)}{\gamma(0)} = \frac{-\sigma_D^2}{\sigma_C^2 + 2\sigma_D^2} \right] \leq 0$$

indicating that the lag-one autocorrelation of the ITIs is negative within the interval [-0.5,0], i.e. errors in the ITIs will, on average, be compensated for in the following interval despite the absence of feedback. The variability of the clock intervals has been found to increase

[2] As sketched in the next section, the Wing-Kristofferson model can be readily extended to accommodate linear drift by modifying the neural clock; this keeps the correlation structure of the detrended ITIs intact.

monotonically with increasing interval duration (or decreasing movement frequency) (Vorberg and Wing, 1996), implying that the ITI variance, $\gamma(0) = \sigma_C^2 + 2\sigma_D^2$, increases as well. Note that the motor delay variance has been found to be constant over different tapping frequencies (Wing and Kristofferson, 1973; Vorberg and Wing, 1996). Hence, the absolute value of the lag-one autocorrelation will decrease with decreasing movement frequency. By using a tapping sequence that involves intentional drift, however, one may probe the clock in a different way than by considering different constant frequencies. By analyzing continuation tapping in this setting, we can examine the generality of the Wing-Kristofferson model.

It is conceivable that the Wing-Kristofferson model may account for tapping with intentional drift by simply recasting the clock interval as $C_i = C_i^{(0)} + \delta \cdot i$, where $C_i^{(0)}$ denotes the base clock interval and δ denotes a finite rate of change in clock interval. In this case, the autocorrelations will match those predicted by the Wing-Kristofferson model. If, on the other hand, additional planning or conscious control is required, this and the added mental load of the drift may cause the autocorrelations to diverge from the Wing-Kristofferson model predictions. As explained above, a monotonic drift cannot be maintained for an extended period of time simply due to neuromechanical constraints; the closer one gets to one's maximal tapping speed, the more attenuated the drift will become, and eventually the increase in tempo will saturate. Such ceiling effects on drift might also cause the autocorrelations calculated from intentional drift sequences to differ from those predicted by the Wing-Kristofferson model.

After correcting for the predictable linear drift in tapping sequences, one is left with an isochronous sequence which can be analyzed in terms of autocorrelations and compared to the timer properties as predicted by the Wing-Kristofferson model for constant frequency sequences. After confirming that the autocorrelations found in this study matched those predicted by the Wing-Kristofferson model, we used the Wing-Kristofferson model to estimate the clock and motor delay variance. Obviously, in the case of intentional drift, the more non-linear the drift, the worse the estimates of these parameters, as will become apparent below.

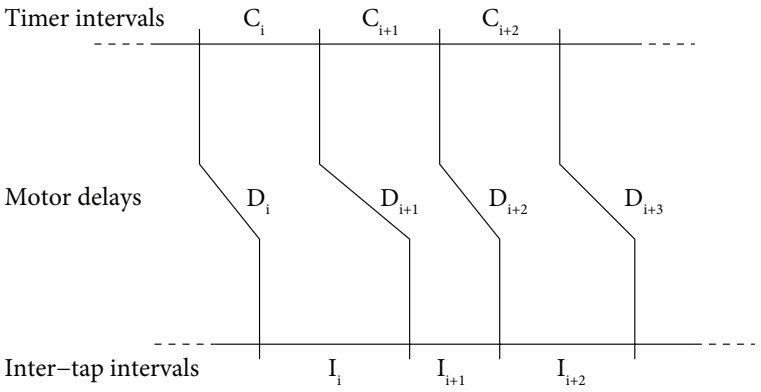

Figure II.1: The two-level timer model proposed by Wing and Kristofferson: C_i denote clock intervals (mean μ_C, variance σ_C^2) and D_i denote motor delays (mean μ_D, variance σ_D^2); inter-tap intervals (ITIs) are defined as $I_i = C_i + D_{i+1} - D_i$ (mean μ_C, variance $\sigma_C^2 + 2\sigma_D^2$).

II.3 METHODS

The experiment consisted of two separate sessions. During the first session, only behavioral signals, i.e. tapping events, were recorded, whereas during the second session surface EMG was recorded as well.

SUBJECTS

In total, 21 healthy individuals without formal musical training participated in the experiment after signing an informed consent form, ten in the first session (five males and five females; age: mean 28.4, SD 4.0 years) and 11 (eight males and three females; age: mean 34.9, SD 8.6 years) in the second session. The experiment was approved by the local ethics committee. All subjects were right-handed according to their scores on the Edinburgh inventory (Oldfield, 1971).

PROCEDURE

The experimental task was a synchronization-continuation tapping task with the right hand. The task was performed in four conditions; three constant frequency conditions (1.5, 2.0, and 2.5 Hz) and an intentional drift condition involving linearly decreasing ITIs

corresponding to an increase in frequency from 1.5 to 2.5 Hz.[3] During the synchronization phase of the intentional drift condition the pacing of the ITIs decreased by 4 ms per tap. Subjects were asked to continue this decrease. The decrease of 4 ms per tap is noticeable at a starting ITI corresponding to 1.5 Hz, as determined by Madison and Merker (2005). The task was performed for 35 s with 10 s of acoustic binaural pacing at the beginning (stimulus: pitch 440 Hz, duration 50 ms). Subjects were verbally informed of the end of each experimental trial. Each condition was presented as a block of six data collection trials. Before starting these trials, the subject practiced the desired frequency or drift by following a completely paced sequence. Halfway through the six data collection trials, the subjects were given 35 s of rest. Each of the four conditions (as a block of six trials) was performed twice, and the order of the frequencies was counterbalanced. Both sets of the intentional drift condition were performed either before or after the constant frequency conditions. This order (before or after) was randomized. The total experiment for each session thus consisted of eight blocks of six data collection trials each.

The protocol was implemented in Labview (National Instruments, Austin, TX, USA). Subjects were seated upright in a comfortable position, with their hands and arms supported by arm rests. Both hands lay flat on the arm rests and the force produced by taps of the right index finger was recorded using a force transducer (sampling rate: 1 kHz for the first set, and 1.25 kHz for the second data set). For the second data set, EMG was recorded from the flexor and extensor of the right index finger (EMG_{flex}: *m. flexor digitorum*, EMG_{ext}: *m. extensor digitorum*) where the ground electrode was positioned on the lateral epicondyle of the right humerus.

II.4 DATA ANALYSIS

The tap events were determined from the force response of the force transducer. Figure II.2 shows a typical force response. The tap event was defined as the start of the sharp increase prior to the force peak. The event detection was minimally influenced by noise, yielding an error of a couple of samples (i.e. a few ms) at most. Only complete tapping sequences, displaying separate force profiles for each tap and without 'misses' (992 out

[3] Pilot studies revealed that subjects had great difficulty increasing their ITIs in a regular, linear fashion, often resulting in a marked decrease in tempo followed by a very slow tapping frequency. Therefore, drift with a decreasing frequency was deemed unsuitable for this study.

of 1,008) were included. For all analyses based on tap events, the continuation phase was used starting 14 s after the start of a trial to avoid adverse effects from the synchronization to continuation transition. For the intentional drift condition this implies that the starting frequency was 1.7 Hz and that the average ITI was 400 ms corresponding to a frequency of 2.0 Hz. From the force profiles, the amount of force per tap was calculated as the area underneath the force profile. ITIs were defined as the time difference between two successive tap events. Figure II.3 shows the ITIs of a trial in the intentional drift condition. Autocorrelation functions for 947 (see below) ITI sequences were computed for trials with a continuation sequence of at least 30 events.

Autocorrelograms of the ITI sequences, covering lags 0 through 7, were calculated using the 30 consecutive taps of each trial that showed the least drift (i.e. where the slope of the linear fit was closest to zero for the constant frequency conditions), and 30 points for each drift trial that showed the smallest deviation from linear drift (in the intentional drift condition). This procedure was followed to eliminate the error in the autocorrelation estimates due to non-linear drift as much as possible. Drift sequences were only included if they showed a total decrease of at least 0.22 Hz (approximately 25% of the target drift) and did not exceed 4 Hz (approximately three times the target drift). In total, 45 sequences were discarded. The resulting 947 sequences were linearly detrended before computing autocorrelations (Doumas and Wing, 2007).

To compare the degree of difficulty of the intentional drift condition to that of the constant frequency conditions, we compared performance errors, in terms of the deviation from the intended ITIs, of the entire continuation part of all 947 sequences. We compared the target change in interval length (0 ms/tap for the constant frequency conditions, -4 ms/tap for the intentional drift condition) to the actual change. For artifact removal the EMGs were band-pass filtered between 10 and 400 Hz (2^{nd} order bi-directional Butterworth). Signals were subsequently used to estimate the physical delay (PhysD), i.e. the time between muscle activation onsets and tap events, which covers the mechanical aspect of the motor delay in the Wing-Kristofferson model. EMG onsets were derived with a generalized likelihood ratio estimator (Micera et al., 1998; Stylianou et al., 2003), using a test function based on the linear envelope of the EMGs. The EMG traces were full-wave rectified to obtain a linear envelope (Myers et al., 2003). For each trial, these EMG traces were averaged over tap events to increase the signal-to-noise ratio. PhysD values were determined for each

trial, and mean and variance values were calculated for each subject and conditions based on these data. The values averaged over subjects are given in Table II.3 as discussed below. A total of 142 trials (out of 512) in which the PhysD could not be determined within a range of 150-50 ms prior to the tap were discarded. In addition to PhysD, we quantified the co-activation of the flexor and extensor muscles via a co-contraction index (CCI), which was calculated for the full-wave rectified EMG traces during the continuation phase as

$$\mathrm{CCI} = \frac{\overline{\mathrm{EMG_{flex}} \cdot \mathrm{EMG_{ext}}}}{\overline{\mathrm{EMG_{flex}}} \cdot \overline{\mathrm{EMG_{ext}}}}$$

where $\overline{\cdots}$ denotes the mean over time.

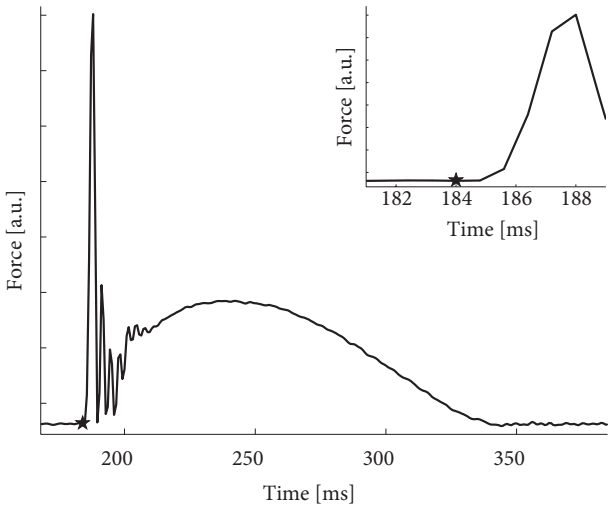

Figure II.2: Typical force profile, with force displayed in arbitrary units (a.u.). The tap event was defined as the start of the sharp increase prior to the force peak as indicated by the asterisk. The inset shows a more detailed view of the same force profile at the time-point of event detection (marked with an asterisk).

STATISTICS

To assess the influence of frequency, one-way repeated measures analyses of variance (ANOVAs) were conducted per outcome variable on the constant frequency conditions for which values were averaged over trials. A significance level of $\alpha = 0.05$ was maintained. The design, given a medium effect-size ($\omega^2 = 0.25$), had a power of 0.73 for analyses

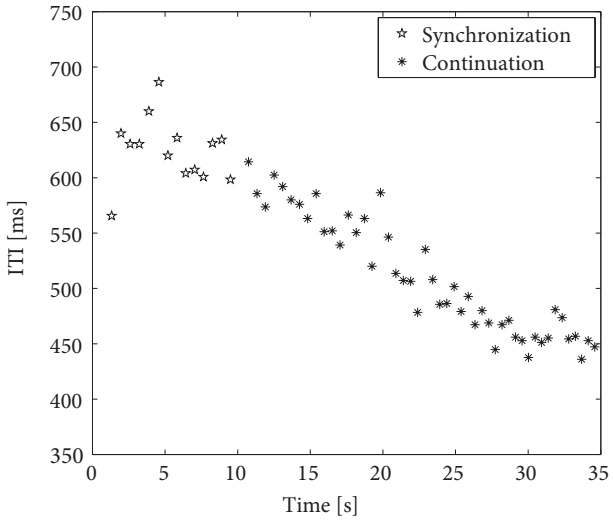

Figure II.3: ITIs during an intentional drift sequence.

involving 11 subjects, and a power of 0.98 for analyses involving 21 subjects. Error-bars in figures represent the standard error.

II.5 RESULTS

The force data from both sessions were pooled. Performance accuracy was measured by the deviation from the intended change in ITI (0 ms/tap for the constant frequency conditions, -4 ms/tap for the intentional drift condition, as shown in Figure II.4).

There was a significant influence of *tapping frequency* on the performance accuracy of the constant frequency conditions ($F_{2,40} = 28.18, p < 0.0001$). As indicated in Section II.1, the intentional drift condition was properly performed but significantly less well than any of the constant frequency conditions ($ps < 0.0001$). Intentional drift is thus considered to be a more challenging sequence to tap than a constant tempo. Tap force profiles became shorter as tapping frequency increased and the total force per tap decreased. This significant change in *force level* was confirmed ($F_{2,40} = 10.41, p < 0.001$) and mean values are summarized in Table II.1. All pairs were significantly different from each other ($ps < 0.05$).

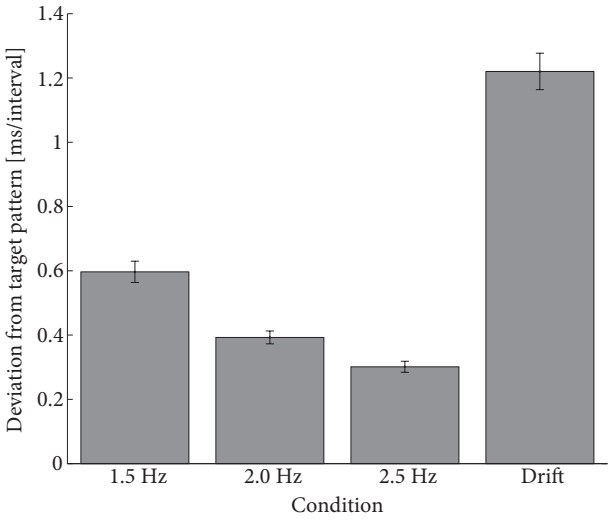

Figure II.4: Performance accuracy as measured by the deviation from the intended change in ITI.

Recall that the ITI variance is known to increase with increasing target interval (e.g. Vorberg and Wing, 1996). Figure II.5 shows the ITI variance for each condition. A significant effect of tapping frequency on ITI variance in the constant frequency conditions was found ($F_{2,40} = 53.09, p < 0.001$). Post hoc tests revealed that all pairs were significantly different from each other ($ps < 0.05$). In the drift condition, this trend was also present. To demonstrate this, the drift data were split into two sets of 15 events each.

As expected, and consistent with the trend found in the ITI variance of the constant conditions, the ITI variance of the slow part of the drift was significantly larger ($t_{19} = 1.99, p < 0.05$) than that of the fast part (see Figure II.5), although the difference was smaller than expected from the values found in the constant frequency conditions.

The 30 events that showed the most constant or most linear behavior were selected from each tapping sequence. The deviation from that constant value or from the linear drift could thus be used to compare the constant frequency conditions with the drift condition. We used the residuals of the linear fit to the data to assess this. Table II.1 displays the means and standard errors of the residuals for each condition. A significant influence of tapping frequency on the size of the residuals was found in the constant frequency conditions ($F_{2,40} = 73.29, p < 0.001$). All pairs were significantly different from each

Table II.1: Force levels, residuals of linear fit to ITI sequences (mean ± std. error, in arbitrary units [a.u.]).

Condition	Force [a.u.]	Residuals [a.u.]
1.5 Hz	72 ± 5	126 ± 31
2.0 Hz	54 ± 4	103 ± 28
2.5 Hz	43 ± 3	86 ± 23
Drift	61 ± 5	93 ± 22

other ($ps < 0.05$). The residuals of the intentional drift condition fell between those of the 2.0 and 2.5 Hz condition. This was expected as the average ITI during the continuation phase of the intentional drift condition corresponded to a frequency of 2.0 Hz, but was often slightly higher. The variance is also similar to the 2.0 and 2.5 Hz conditions (see Figure II.5). The goodness-of-fit showed a similar trend to that found for the ITI variability (see also Table II.1).

Autocorrelograms of the analyzed tapping sequences are shown in Figure II.6. All constant frequency conditions showed a clear negative lag-one autocorrelation and autocorrelation values close to zero for higher lags. Interestingly, the intentional drift condition also showed a clear negative lag-one autocorrelation and small negative values for lags 2 through 4. Larger negative values were found for lags 5-7. Table II.2 summarizes the results of one-sample t-tests performed for each condition for each lag. Significant results at lags 5 through 7 in the intentional drift condition reflected non-linearities in the drift, where the sign and the decreasing values of the autocorrelations at these lags were consistent with a saturation of the drift.[4] Nonetheless, the structures of the autocorrelations were comparable across conditions, where the negative lag-one autocorrelation for the intentional drift condition fell between those for the 1.5 and 2.0 Hz conditions.

As described earlier, we decomposed the ITI variance into clock variance and motor delay variance. In the Wing-Kristofferson model, only the clock variance is supposed to be frequency dependent. However, Doumas and Wing (2007) found a small but statistically significant decrease in motor delay SD for smaller ITIs. In our study, this decrease, although

[4] In the case of saturating ITIs, the detrending will result in later ITIs being smaller than the first ones. Therefore, saturation yields negative autocorrelations and this effect is more pronounced for higher lags.

Table II.2: One-sample t-test p-values for each condition and autocorrelation lag. Significant results are in bold

Condition	Lag						
	1	2	3	4	5	6	7
1.5 Hz	<**0.001**	0.164	0.806	<**0.05**	0.785	0.100	0.120
2.0 Hz	<**0.0001**	0.583	0.671	0.897	0.834	0.554	<**0.001**
2.5 Hz	<**0.0001**	0.259	0.125	0.377	0.762	0.215	0.280
Drift	<**0.0001**	0.231	0.071	0.542	<**0.01**	<**0.01**	<**0.001**

present in the motor delay variance, failed to reach significance ($F_{2,40} = 3.11, p = 0.055$). The effect of frequency on clock variance was significant ($F_{2,40} = 44.66, p < 0.001$) and all pairs were significantly different from each other ($ps < 0.05$). Figure II.7 (panels A1 and A2) shows the values of the model parameter estimates. The influence of tapping frequency on the clock variance estimate was much greater than on the motor delay variance estimate.

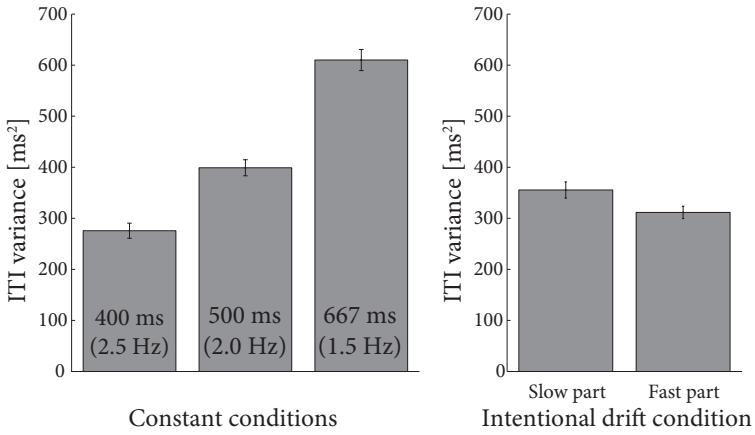

Figure II.5: ITI variance in the three constant frequency conditions and the drift analyzed in a slow and a fast part.

The model parameter estimates of some sequences fell outside the boundaries mentioned in the section on the Wing-Kristofferson model, that is, the lag-one autocorrelation fell outside the interval [-0.5,0]. This was the case for 254 of the 992 trials. When removing those sequences from the analysis (the results for the remaining sequences are

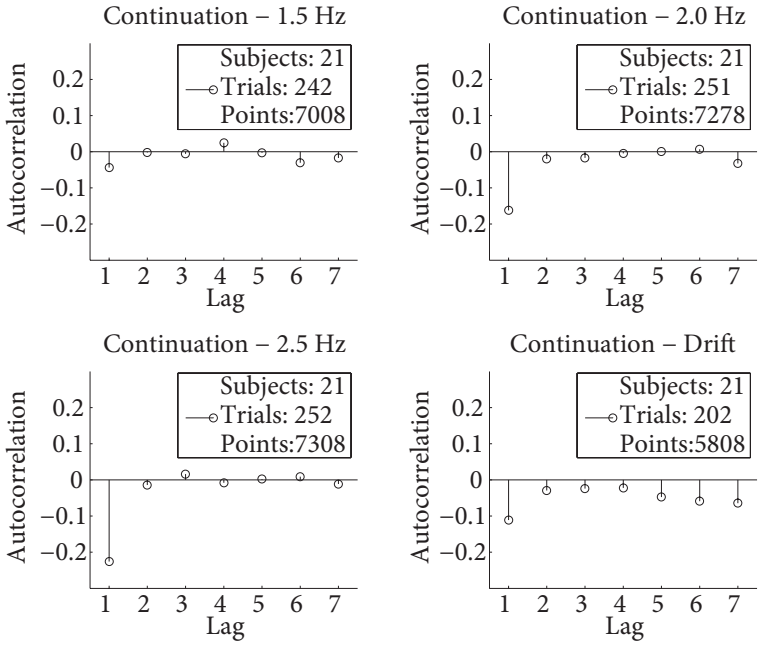

Figure II.6: Autocorrelation function (lag 1-7) for each condition averaged over trials and subjects.

shown in Figure II.7, panels B1 and B2), we found similar results for the timer variance ($F_{2,40} = 32.48, p < 0.001$). Post hoc test revealed that all pairs were significantly different from each other ($ps < 0.05$). In addition, we found a significant influence of tapping frequency on the motor delay variance, where, in line with Doumas and Wing (2007), shorter tap intervals had a smaller value for the motor delay variance σ_D^2 ($F_{2,40} = 5.20, p < 0.05$). The motor delay variance at 1.5 Hz was significantly larger than at 2.5 Hz, and the motor delay variance at 2.0 Hz was larger than at 2.5 Hz ($ps < 0.05$).

To examine the influence of tapping frequency on motor variance we used the EMG_{flex} signals. One can assume that the motor delay has a neural and a mechanical component. In view of the brevity of the neural delay between primary motor areas and proximal muscles, in particular the finger flexors (Nezu et al., 1999), we assume that the larger part of the motor delay will be the time from neural activation of the muscles to the actual tap, including the movement time of the index finger. As the amount of force per tap is dependent on tapping frequency, the PhysD may also depend on tapping frequency. A significant influence of tapping frequency in the constant conditions on PhysD was found

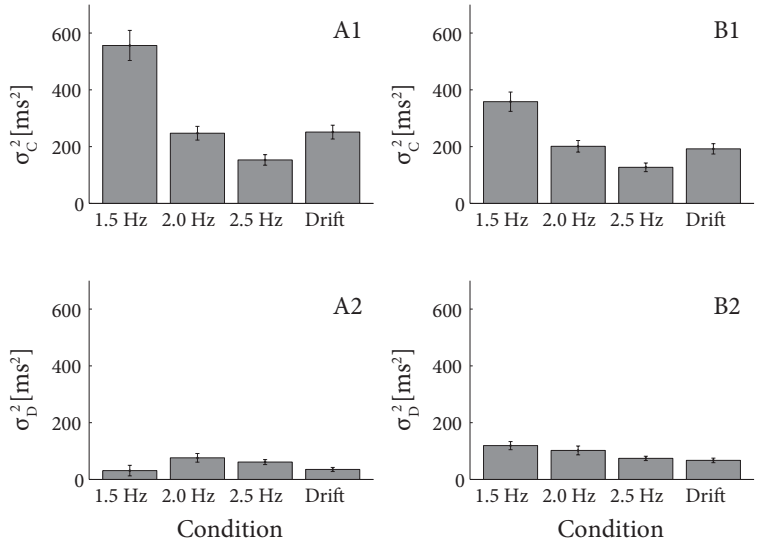

Figure II.7: Model parameter estimates per condition. Timer and motor delay variance when all sequences are considered (panels A1 and A2), and when only sequences are considered that adhere to the Wing-Kristofferson boundaries (panels B1 and B2).

($F_{1.10,7.77} = 6.841, p < 0.05$, Greenhouse-Geisser correction). In contrast, there was no significant influence on PhysD variance ($F_{1.04,7.3} = 0.39, p = 0.559$, Greenhouse-Geisser correction), although there was a trend in that the PhysD values tended to increase. PhysD and PhysD variance values are given in Table II.3. PhysD during intentional drift was comparable to levels found in the constant frequency conditions. There was no clear relation between tapping frequency and PhysD variance.

Table II.3: Physical delay (PhysD) mean and variance.

Condition	$PhysD_{mean}$ [ms]	PhysD variance [ms^2]
1.5 Hz	92	585
2.0 Hz	113	334
2.5 Hz	119	428
Drift	102	463

We found a significant influence of tapping frequency on CCI ($F_{2,20} = 8.77, p < 0.005$), indicating a reduction of co-activation of the flexor and extensor muscles at higher tapping frequencies (Figure II.8). CCI was larger at 1.5 Hz than at both 2.0 Hz and 2.5 Hz ($ps < 0.05$). Muscle co-activation during intentional drift was comparable to levels found in the constant frequency conditions.

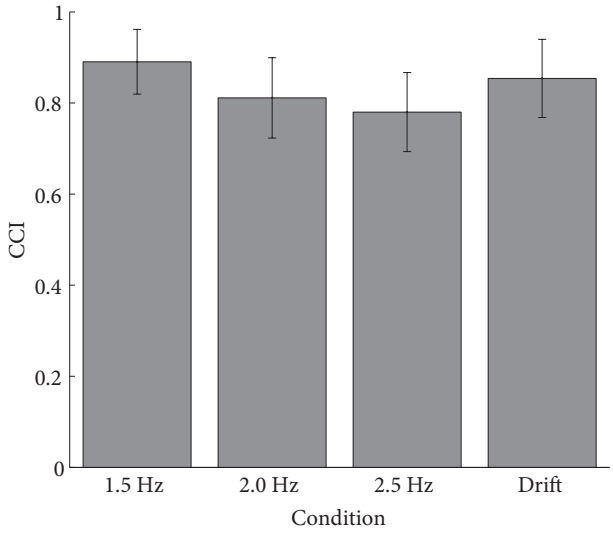

Figure II.8: CCI for each condition.

II.6 DISCUSSION AND CONCLUSION

Here, we studied rhythmic tapping with and without intentional drift to examine the generality of the Wing-Kristofferson model and properties of neural timing in general. For this purpose, we compared parameter estimates of the Wing-Kristofferson model and additional measures (force, lag-one autocorrelation, ITI variability, PhysD, and muscle co-activation) across experimental conditions. We were especially interested in the comparison between tapping at a constant frequency and tapping at a continuously increasing frequency because the time base of the neural clock may be assumed to be fixed in the former case and must be continuously adjusted in the latter. In this light, it was not surprising that subjects reported the intentional drift condition to be much more difficult to perform than tapping a constant tempo. In line, and as expected on the basis of a pilot study, we found that performance

was less accurate for the intentional drift condition. However, in spite of these differences between tasks, we found that most variables, after compensating for the drift by linear detrending, were similar, if not identical, for tapping with intentional drift and tapping at a constant tempo. This general result implies that the basic partitioning of continuation tapping into a clock interval and a motor delay, which is inherent to the Wing-Kristofferson model, does not only describe isochronous tapping but also adequately describes tapping linearly decreasing intervals. Moreover, the temporal properties of the underlying timing processes are similar across conditions.

Task difficulty in terms of motor planning, control, and mental load might have influenced the temporal properties, as reflected in the autocorrelations, of the timer responsible for producing the tapping sequences. We have established that the intentional drift task was performed less well than constant tapping. However, since temporal properties matched across conditions, we can conclude that (experienced) task difficulty is not manifested in the timing of motor performance. We therefore conclude that, as the Wing-Kristofferson model adequately describes the intentional drift task, the decomposition of ITIs into a clock interval and a motor delay as implied by the Wing-Kristofferson model is properly extended to this task as well. We may even speculate that this result may be extended to non-linear (largely) deterministic drifts. Equivalent to the linear case, the model's clock intervals may be replaced by $C_i = C_i^{(0)} + \delta(i)$ with $\delta(i)$ denoting an arbitrary function that depends on the interval number i, i.e. on time. Subtracting that function from the ITI sequence, that is, detrending the ITIs, will recover the negative lag-one autocorrelation as implied by the Wing-Kristofferson model.[5]

However, a number of properties warrant further discussion. The negative lag-one autocorrelation was closer to zero than expected during intentional drift. The most likely explanation of this finding is that subjects did not perform a purely linear drift. There is evidence that drift perception is governed by a detection threshold for a change in tempo (e.g. Madison, 2001). If drift production involves a similar process, drift would show abrupt changes and would not be linear and monotonic. As a consequence, the detrending procedure applied here would have been insufficient to compensate for the ensuing nonlinearities in the produced drift. Madison (2001) showed that this kind of influence results in lag-one autocorrelation estimates closer to zero (i.e. less negative than the Wing-Kristofferson

[5] Instead of $\delta(i)$ one may also use an arbitrary but known, discrete sequence δ_i.

model predicts). Despite the deviations from linearity and the fact that drift can be modeled in a variety of ways (Madison, 2001; Collier and Ogden, 2004), the linear fit found here was well within the range of the constant frequency conditions, implying that the subjects followed the instructions to a satisfactory degree.

Irrespective of the lower performance accuracy (in terms of the deviation from the intended change in ITI) during the intentional drift condition due to the greater difficulty of this pattern, the ITIs used in the analysis did not show higher variability than that found in the constant frequency conditions. In contrast, Doumas and Wing (2007) found a higher variability for a more difficult task (tapping a rhythm), indicating that tapping with an intentional drift is more similar to tapping at a constant pace than tapping a particular rhythm. It is possible that, although there is a need for more involved planning in this task, movement execution does not interact with this planning. In that case, any perceived difficulty due to planning would not transfer to tapping behavior. A recent study by Lewis et al. (2004) supports this interpretation as initiation, synchronization, and continuation were found to be affected in different ways during the performance of tasks with different degrees of difficulty. On the other hand, because our subjects had no musical training, it is possible that they were not able to make on-line corrections during their performance. By asking well-trained musicians to perform the same task, it might be possible to gain insight into this matter.

Besides broadening the class of tapping behaviors described by the Wing-Kristofferson model, the present study produced several insights into the clock and motor aspects of isochronous and non-isochronous tapping, which we discuss in turn, starting with the motor aspects. An unresolved issue with regard to the motor delays is whether their variance depends on the tapping frequency. Whereas the Wing-Kristofferson model assumes that this is not so, a recent study reported a small but significant dependence (Doumas and Wing, 2007). In the present study, we found a similar dependence, at least when the analysis was confined to tapping sequences with lag-one autocorrelations within the interval [-0.5,0] predicted by the Wing-Kristofferson model. Given that the Wing-Kristofferson model only provides an estimate of the variance of the motor delay, we attempted to estimate part of the motor delay by analyzing the PhysD and its variance, but with inconclusive results. We also analyzed the level of muscle co-activation and found a significant influence of tapping frequency on CCI. In addition, like Sternad et al. (2000), we found that the amount

of force per tap was smaller for higher tapping frequencies. All in all, the evidence for an influence of tapping frequency on PhysD appears mixed and, as it stands, inconclusive. Yet, considering that muscle-tendon complexes have non-linear, time-dependent relationships (Spanjaard et al., 2009), and that movement trajectories depend on tapping frequency (Doumas and Wing, 2007), we believe it is likely that motor delays and their variance do depend on tapping frequency, at least to a degree.

As regards the clock aspects, the Wing-Kristofferson model does not address the neural organization of the timer. It is difficult, if not impossible, to gain insight into this aspect solely from behavioral data (Wing, 2002). From imaging studies we know that multiple brain areas are involved in motor timing tasks in a task-dependent fashion (Mayville et al., 2005; Turner et al., 2003). In view of the discussed differences between constant frequency tapping and tapping with intentional drift, it is therefore rather likely that different networks were involved in both forms of tapping, potentially controlling repetitive movements with different temporal properties. Hence, we find it remarkable that the behavioral properties of interest were so similar between isochronous and non-isochronous tapping. This finding speaks for the existence of an, abstractly defined, neural timer with invariant characteristics that are preserved over different task instantiations. Whether this is indeed the case remains to be established because, in principle, it is conceivable that differences in neural assembly processes are washed out when transferred to motor output. To resolve this issue it is necessary to study the connection between brain activity and motor output, including the total delay between the central timer and the motor output, as well as their variances. A promising approach might be an assessment of neural activation with high temporal resolution, e.g. with encephalographic recordings, with an additional source localization to estimate activities in subcortical areas, basal ganglia, the cerebellum, etc., in conjunction with detailed motor output recordings.

II.7 ACKNOWLEDGMENTS

We would like to thank the Netherlands Organisation for Scientific Research for financial support (NWO grant #452-04-344).

CHAPTER III

DIFFERENTIAL AFTER-EFFECTS OF BIMANUAL ACTIVITY ON MIRROR MOVEMENTS

Abstract

Using a rhythmic isometric force production paradigm, we investigated the after-effects of in-phase and anti-phase bimanual performance on the unintended recruitment of the homologous muscles of the opposite limb during subsequent performance of tasks that were unimanual by design. Electromyograms obtained from the muscles of the opposite limb were analyzed in terms of their amplitude and the distribution of their phase relative to that of the intended movements. Preceding bimanual activity had distinct effects on the relative phase (mean and uniformity) of the structured electromyograms. These were particularly pronounced following performance of the in-phase pattern. These findings are discussed in terms of interhemispheric excitation and inhibition.

Adapted from:

A. N. Vardy, A. Daffertshofer, A. Ridderikhoff, and P. J. Beek, Differential after-effects of bimanual activity on mirror movements. *Neurosci Lett*, 416(2):117-122, 2007.

III.1 INTRODUCTION

Mirror movements (MMs) are unintended activities of homologous muscles on the opposite side of the body during intended unimanual performances that are also referred to as (contralateral) motor irradiations (Cernacek, 1961), motor overflows (Armatas and Summers, 2001; Bodwell et al., 2003), synkinesis (Hwang et al., 2005), or associated movements (Lazarus and Todor, 1991). While MMs are frequently observed in pathologies like hemiparesis, X-linked Kallmann's syndrome (Mayston et al., 1997), and after stroke (Hwang et al., 2005), they are also manifest in healthy subjects, in particular young infants – (see e.g. McDowell, 2003, for a recent review). Expressions of MMs in healthy subjects typically diminish with development and it is commonly stated that they disappear around the age of 10 (see e.g. Duque et al., 2005). However, they may persist in adulthood (Mayston et al., 1999) and can even become rather pronounced in the elderly (Bodwell et al., 2003). Interestingly, MMs are modulated by the nature of the performed activity (Armatas and Summers, 2001). Generally speaking, the more difficult a task becomes, the more likely that involuntary movements will occur; an increase in movement tempo (or rate in rhythmic tasks) may increase occurrence (Bodwell et al., 2003) and so does an increase in contraction level of the moving hand (Armatas et al., 1996; Todor and Lazarus, 1986). Also, motor overflows may be influenced by hand dominance (Liederman and Foley, 1987) in that intended movements of the less dominant hand may yield more pronounced MMs in the dominant hand than vice versa.

We examined distinct influences of performing different unimanual and bimanual tasks on MMs that occurred during subsequent unimanual tasks, with preceding unimanual tasks serving as control conditions. Subjects were invited to perform in-phase and anti-phase coordination patterns (IP, i.e. simultaneous activation of homologous muscles, and AP, i.e. alternating activation of homologous muscles, respectively). IP and AP can be quantified via the relative phase between moving or force-producing limbs. IP refers to a relative phase of 0°, whereas AP implies a left/right phase difference of 180°. AP is known to be more difficult to perform than IP, in particular when performance tempo is high (Kelso, 1995). Likewise, MMs may exhibit a unimodal distribution of relative phases indicating that MMs occur predominantly in phase with the intended movement. The prominence of in-phase MMs suggests a strong relation between MMs and bimanual coordination and may be associated with the higher stability of in-phase coordination (Daffertshofer

et al., 1999; Ridderikhoff et al., 2005). To investigate possible relations between MMs and coordination patterns we looked for the presence of after-effects of IP and AP coordination on MM properties in subsequent unimanual tasks. In view of the aforementioned similarity between phase distributions of coordination patterns and MMs, we expected the subsequent MMs to reflect the phase relationship that characterized the previously performed bimanual pattern (i.e. IP versus AP). We also expected the induced changes in MM patterns to shed light on interhemispheric interactions underwriting rhythmic bimanual coordination (see e.g. Swinnen, 2002), and to strengthen, in so doing, the apparent link between MMs and bimanual coordination.

III.2 METHODS

SUBJECTS

Twelve healthy individuals, seven males (age: 27.6 $\pm$ 4.6 years, mean $\pm$ SD) and five females (age: 26.2 $\pm$ 3.3 years), participated in the experiment after signing an informed consent form. The experiment was approved by the local ethics committee. Handedness was assessed using the Edinburgh inventory (Oldfield, 1971). Three male subjects were excluded from further analyses: one subject could not be classified as either left or right handed (L.Q. =-33, Decile L.2), another (right-handed) subject was excluded for not having followed the procedure, and for a third (right-handed) subject we were unable to determine two distinct frequencies for stable performance (see below). All analyzed subjects were right-handed.

The electromyogram (EMG) was chosen to identify MMs as, in particular, in isometric tasks it allows for rather sensitive detection even when force production of the middle finger is too subtle to be determined or absent due to co-contraction of its antagonistic flexor and extensor muscles. Using EMG also renders misclassification due to biomechanical disturbances unlikely. We recorded the surface EMG for both left and right *m. extensor digitorum communis* and sampled at 2 kHz (TMS International, Porti5-16/ASD; 22 bits ADC). After skin preparation, two electrodes (bipolar configuration) were placed above the muscle belly. The common mode electrode was placed above the lateral epicondyle of the left humerus. Force was recorded using two force transducers (SCAIME, F30X 100). Subjects were asked to place their hands palms down on rests placed on a table-top. Their

wrists were fixated to avoid force production with the forearms and to reduce the (remote) possibility of mechanical crosstalk. The fingers were fixated to the force transducers to ensure proper force conduction during upward (extension) force production as well as subject's comfort. Visual feedback was provided for both hands separately on a computer monitor: produced force level, averaged over 1 s, was updated every second to avoid additional phase information. Subjects also received visual warnings if force production was too low or too high. Auditory pacing (stimulus duration: 50 ms, pitch: 200 Hz) was presented through speakers and subjects were asked to synchronize peak extension force with the metronome during unimanual and IP performance. During AP performance, only the right hand was paced.

PROCEDURE

Subjects received instructions about the experiment but were not aware that MMs were at issue. Three practice trials were performed in which subjects were asked to exert force with their middle fingers in anti-phase in time with an auditory pacing signal. Subjects were instructed to generate force 'smoothly' (extension only) at an average of 15% F_{max} as guided by visual feedback and, simultaneously, to keep timing accurate. Four different tasks were performed: AP (fingers producing force in alternating fashion), IP (fingers producing force simultaneously), LF (left middle finger only), and RF (right middle finger only). After practice of the AP task at 1.6 Hz, F_{max} and corresponding maximal voluntary contraction (MVC) values of the muscles involved were determined by simultaneously exerting maximal force with both fingers. Every subject produced maximum force for 5 s. F_{max} was defined as the maximally achieved peak force over three consecutive attempts and MVC was determined via the root mean square of the corresponding EMG. Percentages of F_{max} were provided as visual feedback during the experimental session. Target levels were displayed visually and warnings were given if the averaged force levels exceeded 25% or dropped below 15% MVC. All subjects were able to meet the 15% F_{max} target.

Because AP was deemed difficult (since performance of this coordination pattern may become unstable as movement frequency is increased), stable low and high performance frequencies were determined by two ramp trials, during which the AP pattern was performed at ten frequencies increasing from 1.2 to 3.0 Hz in 0.2 Hz steps (15 s of performance and 5 s of rest per frequency to ensure the subject's comfort). Low and high pacing frequencies were determined by visual inspection of the force time series. The low frequency

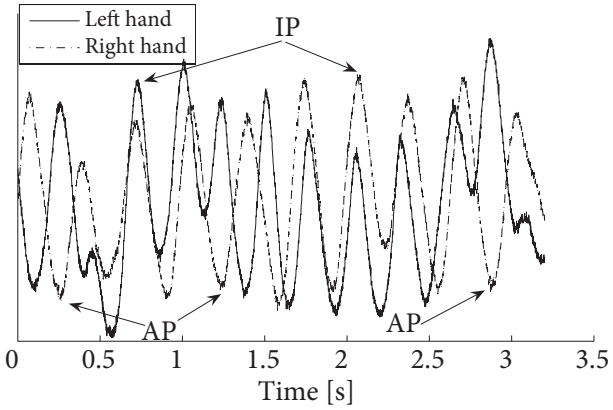

Figure III.1: Unstable force production during anti-phase (AP) performance at 2.8 Hz. Two switches from anti-phase to in-phase (IP) and back again are shown. Transitions during bimanual performance reflect a loss of stability of the prevailing coordination pattern (Haken et al., 1985).

was defined as the frequency at which performance was optimal in that fluctuations of the relative phase of the left and right force production patterns were smallest. The high frequency was defined as the critical frequency, i.e. the highest frequency at which the subject's AP performance did not switch to IP coordination (or showed other instabilities), as illustrated in Figure III.1. In the collected data, we observed only brief 'escapes' from AP performance, possibly due to the isometric nature of the task (Carson, 1995). The obtained low and high frequencies were used as pacing frequencies during the experimental sessions.

Every trial consisted of three tasks (see Table III.1) and subjects were informed about the task sequence beforehand. The data from the first, second, and third task represented the pre-test data, the experimental stimulation, and the post-test data, respectively. The first and third task lasted 30 s and the second task lasted 20 s. The tasks were separated by 5 s of rest and an additional minute of rest was provided after each trial. Table III.1 summarizes the eight different conditions that were performed twice for both the low and high pacing frequency. That is, the experiment consisted of $8 \times 2 \times 2 = 32$ trials, which were conducted in four blocks of eight trials. Trial blocks alternated in pacing frequency. Conditions (for each block and subject) and starting frequency (for each subject) were counterbalanced.

All tasks were performed at a target of 15% F_{max}. Since 5 min breaks were given between blocks, a complete session lasted about 2.5 hours.

Table III.1: Experimental design. The first four conditions provided the data for investigating the effects of bimanual performance, while conditions 5 and 6 provided the data for examining effects of ipsi- and contralateral unimanual performance. The other two conditions served to mask the purpose of the experiment. Each condition consisted of a combination of three of the following tasks: anti-phase (AP), in-phase (IP), left middle-finger only (LF), and right middle-finger only (RF). $Task_1$ and $Task_3$ lasted 30 s each and $Task_2$ 20 s. All tasks were separated by 5 s of rest and a minute of rest was provided at the end of each trial.

Condition	$Task_1$ rest (5 s)	$Task_2$ rest (5 s)	$Task_3$ rest (1 min)
	Pre	Stim	Post
1	LF	AP	LF
2	LF	IP	LF
3	RF	AP	RF
4	RF	IP	RF
5	LF	RF	LF
6	RF	LF	RF
7	AP	IP	AP
8	IP	AP	IP

III.3 DATA ANALYSIS

Force data were only used for on-line feedback (see above) and thus need no further discussion. Off-line analyses were realized using Matlab R14 (The Mathworks, Inc. Natick MA, USA). EMG signals were band-pass-filtered (10-400 Hz) using a 2^{nd} order bi-directional Butterworth filter to remove movement artifacts. Subsequently, EMGs were full-wave rectified using the absolute value of the Hilbert transform.

We employed a detection method described in Ridderikhoff et al. (2005), which exploits the Gabor transform to identify epochs of phase- and frequency-locked EMG activity between active and inactive hand. The Gabor transform of a time series $x(t)$ is a modified, time-resolved Fourier transform given by

$$G_a(t) \propto \int x(\tau) e^{-\frac{(\tau-t)^2}{4a^2}} e^{i\omega\tau} d\tau$$

in which the parameter a defines the width of a bell-shaped time window (we set a equal to four movement cycles). Since the transform depends on both time (t) and frequency (ω), it enabled us to study the EMG at the performance (or pacing) frequency as well as its changes over time. This method detected epochs of MM activity varying in length as multiples of four (consecutive) movement cycles. MM occurrence is presented as the percentage of total number of movement cycles that contained MMs.

The processed EMGs were used to calculate the amplitude of a MM here defined as relative maximal voluntary contraction (rMVC):

$$\text{rMVC} = \frac{\%\text{MVC}_{\text{inactive hand}}}{\%\text{MVC}_{\text{active hand}}} \times 100\%$$

As suggested by Todor and Lazarus (1986), we controlled for MVC levels to compensate for possible differences between limbs. The %MVCs of the EMGs at MM instances were determined as root mean squares, calculated over these periods, divided by the corresponding MVC (see above).

In addition to MM occurrence and rMVC, we also measured the relative phase of the MMs per cycle – see (Ridderikhoff et al., 2005) for more details. For pre- and post-test trials, we computed relative phases $\{\phi_1, \ldots, \phi_n\}$ of each cycle during MM epochs per condition. The relative phase of a MM was defined as difference of Hilbert phases of the filtered EMG (corresponding to each detected epoch) of the active and inactive hand averaged over a cycle. We summarized the sets of the so determined phases by their corresponding distributions, circular means (CMs), and phase uniformities (PUs), where PU is a measure of variability taking values in the interval [0, 1], with higher values corresponding to lower variability of relative phases (Batschelet, 1981).

The first four conditions were used to investigate effects of bimanual performance, whereas conditions 5 and 6 served as the basis of the analysis of effects of ipsi- and contralateral unimanual performance (see Table III.1). The remaining two conditions (7 and 8) were implemented only to mask the purpose of the experiment, ensuring that subjects were provided with both unimanual and bimanual performance for tasks 1 and 3. Statistical testing was performed on pooled data.

STATISTICS

MMs were not detected in every trial of each subject. To avoid such missing values, per pair of data sets we only used subjects that showed MMs in corresponding (pre versus post) data sets. As the MM occurrence, rMVC, and PU data sets all violated the assumption of normality, we applied the Wilcoxon signed rank test. In contrast, we used a two sample Kuiper's test (Upton and Fingleton, 1989) for comparing two distributions of circular data (i.e. relative phase distributions). This test is, in general, more sensitive to local differences than a mean or median comparison. The significance level was set to $\alpha = 0.05$. Both tests were performed on pooled data to determine differences in selected variables. We examined the following three data pairs: 1: pre- versus post-unimanual stimulation (conditions 5 and 6), 2: pre- versus post-AP performance (conditions 1 and 3), and 3: pre- versus post-IP performance (conditions 2 and 4). As expected, no significant difference was present between the pre-test data sets for any variable.

III.4 RESULTS

We found no significant effects of active (left/right) hand on MM occurrence. Likewise, we found no significant effect of performance speed, although task difficulty increased with pacing frequency. The differences between pre- and post-test data are summarized in Figure III.2. We found an increase in MM occurrence following IP performance ($p < 0.01$), but no significant influence of unimanual or AP performance. Irrespective of stimulation type we found no significant influences of stimulation on MM amplitude (rMVC).

Unimanual stimulation showed no significant influences on occurrence, CM, PU, or relative phase distributions. Both AP and IP performance showed significant influences on CM (both $p < 0.05$) and relative phase distribution (AP: $p < 0.05$, IP: $p < 0.005$). In both cases, CM was more in-phase orientated after stimulation than before stimulation. Confirming earlier findings (Ridderikhoff et al., 2005), in-phase components prevailed in MM relative phase distributions. Additionally, IP performance significantly affected occurrence and PU (both $p < 0.01$). In general, we found that unimanual stimulation did not influence any of the MM properties. Only bimanual stimulation showed significant influences, in particular after IP performance.

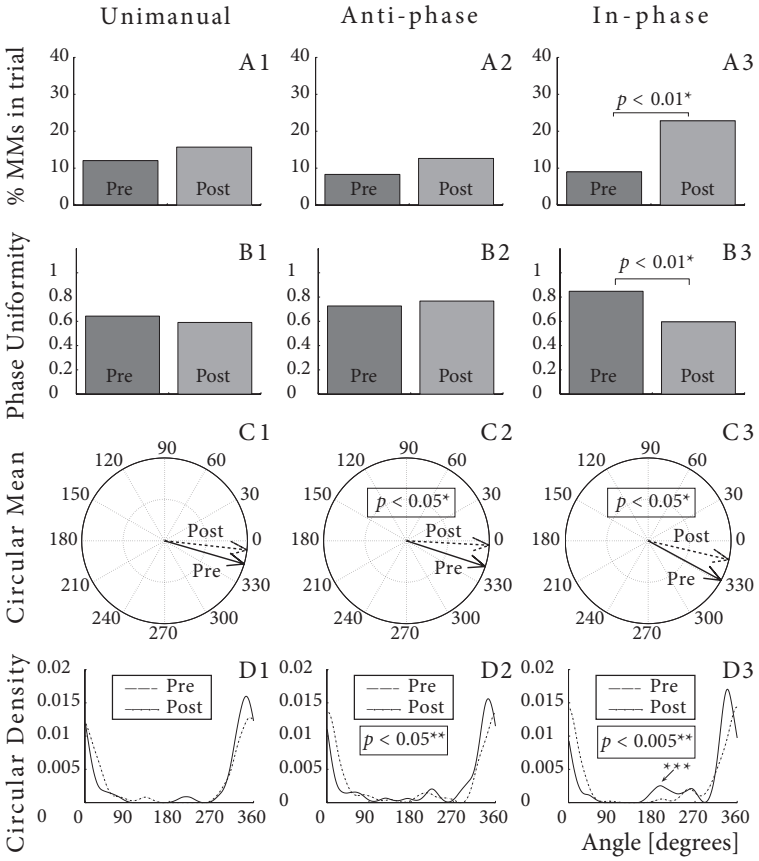

Figure III.2: Results grouped by variable; A1-A3: MM occurrence, B1-B3: phase uniformity, C1-C3: circular mean of pooled phase values, and D1-D3: relative phase distribution of pooled phase values. All variables evaluate influences of (1) unimanual stimulation, (2) anti-phase stimulation, and (3) in-phase stimulation. Results marked with * were significant on the Wilcoxon signed rank test. Results marked with ** were significant on the two sample Kuiper's test. Only bimanual stimulation yielded significant influences, with IP performance providing the greatest influence. The arrow in panel D3 marked with *** highlights a reduction of mass at 180°after IP performance. This decrease is accompanied by an increase of mass around 0°. The increase around 0°was more spread out as was indicated by a reduction in PU; see panel B3.

The main effect of the bimanual stimulation on the MM relative phase distribution was the shift in the in-phase component, as depicted in Figure III.2. IP performance, however, caused an additional effect in that after stimulation the mass around 180°decreased

markedly (Figure III.2, panel D3). Comparing the post-AP and post-IP performance data (see Figure III.3), we observed rather organized differences between phase distributions. The post-AP performance distribution contained more mass than the post-IP distribution at relative phases with values between 12°and 233°(almost a semicircle as denoted by the black area in Figure III.3), whereas the post-IP performance phase distribution contained more mass than the post-AP performance distribution on the complementary semicircle (as denoted by the white area in Figure III.3), conveying the relative phase of the preceding bimanual stimulation.

III.5 DISCUSSION

To recapitulate, using a pre-post test design we derived MM occurrence, amplitude, CM, PU, and relative phase distribution of unintended muscle activity during unimanual performance. We found that unimanual tasks did not yield after-effects on these variables. Bimanual tasks, on the other hand, induced several marked after-effects. (i) Both IP and AP performance affected relative phase distribution and CM. (ii) IP performance also affected MM occurrence and PU. (iii) Focusing on the relative phase distributions after the two types of bimanual stimulation, we found that these differed at specific angles resulting from a decrease in density mass around 180°after IP performance. These findings led us to conclude that different types of stimulation may have indeed distinct effects on MM behavior and that the phase relationship that characterizes the preceding contractions has a reliable impact.

We did not find any significant influences of active hand. However, this was unlikely, because we controlled for F_{max} levels of left and right hand (for which MVC levels were similar), and our target force levels were low (15% F_{max}), reducing the likelihood of asymmetries to emerge (Todor and Lazarus, 1986). Also absent were influences of performance speed even though pacing frequencies ranged from 1.4 to 2.8 Hz. Indeed, an increase in MM occurrence at high performance speed was found in (Bodwell et al., 2003), although subjects did not fall within the age group examined in the present study.

Neural pathways that are possibly associated with MMs are certainly varied and intricate. Nevertheless, the origin of MMs is likely to be cortical, i.e. residing in motor areas contralateral to the inactive hand (Carson, 2005), as we may readily relate our findings

to excitation or excitability of the motor cortex. After all, we found more MMs (more ipsilateral cortical activity) after IP performance, suggesting a prolongation of structured bilateral motor cortex activity after both cortices were simultaneously active. This effect was absent after both unimanual and AP performance. Relative phase densities revealed that in-phase MMs were more frequent than anti-phase MMs. Here, we can infer a higher probability of 'in-phase cortical activity'. Interestingly, the time scales of the two effects, prolonged excitability and preference of in-phase cortical activity, can be considered quite different. While the first lasted at least (part of) the duration of the subsequent unimanual activity but most likely not (far) beyond that duration, the second effect is inherent to MMs. This can be seen in both pre- and post-test presented densities that showed a preference for in-phase MMs (see Daffertshofer et al., 1999; Ridderikhoff et al., 2005). From this finding we conclude that interhemispheric interaction (as discussed in Carson, 2005), bimanual coordination, and MMs are closely related phenomena with common neurophysiological underpinnings.

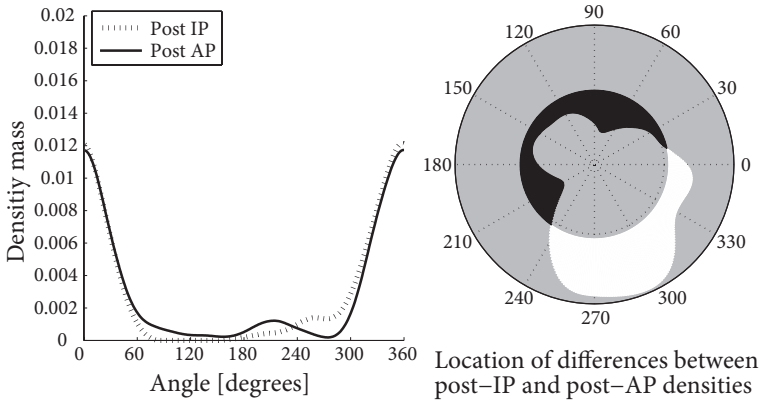

Figure III.3: Left panel: smoothed post-AP and post-IP performance relative phase distributions. Right panel: circular plot of the difference between the post-IP and post-AP performance relative phase distribution, indicating the differential effects of the IP and AP performances on the relative phasing of the MMs; the post-AP performance contained more mass than the post-IP performance distribution between 12°and 233°(black area). In the complementary semi-circle, the post-IP performance distribution was dominant (white area), indicating an influence of the relative phases of stimulation types.

III.6 CONCLUSIONS

Our findings can be explained in several, not mutually exclusive, ways. In closing it is useful to briefly sketch the two main accounts and their respective potential. First, when a voluntary movement is initiated on one side of the body, the corresponding cortical region in the contralateral hemisphere becomes active and facilitates activation of the homologous area in the ipsilateral hemisphere via the corpus callosum (Cernacek, 1961). This transcallosal facilitation results in unintended movement of the homologous limb, i.e. a mirror movement. Second, unimanual movements are 'special' forms of bimanual ones in which one side is inhibited. On this account MMs consist of a (temporary) reduction or failure of inter-hemispheric inhibition (Daffertshofer et al., 2005). As in-phase performance does not require inhibition, one might expect MM behavior to reflect IP coordination. Patently, both ideas are not mutually exclusive as facilitation can be the result of a lack of inhibition. As it stands, both accounts could provide a basis for explaining our findings. However, for both accounts, more detailed neurophysiological data in conjunction with more detailed modeling are required to explain the different effects of IP and AP performance. Furthermore, it is imperative that inhibition (or lack thereof) can, for a period of time, outlast performance, evidence for which is available (Gorsler et al., 2004).

III.7 ACKNOWLEDGMENTS

The Netherlands Organisation for Scientific Research (NWO) financially supported this study (NWO grant #452-04-344).

CHAPTER IV

MOTOR-INDUCED AFTER-EFFECTS AND ATTENTIONAL CHANGES ARE REFLECTED IN BILATERAL M1 IN PARKINSON'S DISEASE

Abstract

External rhythmic cueing can improve motor performance in patients with Parkinson's disease (PD). To uncover the neural underpinnings of this effect, we examined the cortical activity following rhythmic force production without cueing, or with regular or irregular cueing, using magnetoencephalography. Tasks were designed such that PD patients and healthy controls could execute them equally well, ensuring that differences in neural activity were not caused by performance differences. During rest 5 to 10 s after performance we found increased beta activity depending on presence and type of cueing in both PD patients and controls. We also found a late and sustained effect in the alpha band that differed markedly between groups: the alpha amplitude increased significantly 40 s after movement termination in the controls but not in the PD patients. The absence of an increase in power in PD patients may reflect a motor perseverance phenomenon independent of cueing type, suggesting that motor activity may have longer lasting effects in PD than traditionally assumed.

Adapted from:

A. N. Vardy, E. E. H. van Wegen, G. Kwakkel, H. W. Berendse, P. J. Beek, and A. Daffertshofer, Cueing-dependent after-effects of motor performance in bilateral M1 in Parkinson's disease. *Under review*.

IV.1 INTRODUCTION

Parkinson's disease (PD) is a multisystem disorder that comprises both motor and non-motor dysfunction (Wolters et al., 2007). The movement-related problems are believed to originate from disturbances in the circuitry between thalamus, basal ganglia, and primary motor cortices (DeLong and Wichmann, 2007). Timing of automatic movements such as gait is problematic in PD as patients have difficulties initiating, executing, and terminating movements, like an inability to start or abort walking Hallett (2008). These movement disorders can undermine daily functioning and increase dependence on caregivers. Methods for improving motor activities such as gait are therefore of great interest.

Of note in this context are the beneficial effects of external *cueing* in PD (van Wegen et al., 2006; Nieuwboer et al., 2007; Lim et al., 2005a). For instance, when provided with rhythmic auditory, somatosensory, or visual cues, PD patients walk faster with more regular and larger steps (van Wegen et al., 2006; Lim et al., 2005a; McIntosh et al., 1997; Kwakkel et al., 2007; Thaut et al., 1996; Morris et al., 1996; Lewis et al., 2000). However, why external cueing improves motor performance in PD, and how it influences brain activity is largely unknown. Cueing may serve as an external clock that compensates/augments the defective internal rhythm of the basal ganglia (Thaut et al., 1996; Morris et al., 1996), or bypasses the affected neural circuitry resulting in altered neural activity patterns during rhythmic movements in PD (Brooks, 2001; Hanakawa et al., 1999; Haslinger et al., 2001), but the precise neural foundation of cueing remains to be uncovered.

To examine effects of different types of stimuli on cortical activity following a motor timing task, we compared sequences of regular cues with sequences of irregular cues that have a small but noticeable variation (jitter). There was also a self-paced control condition. These conditions can differentially affect brain activity. Here, we focused on brain activity during rest because several studies have successfully employed this method to assess effects of PD (see e.g. Eidelberg, 2009, Piccini, 2004 for a review, Wu et al., 2009 for a very recent study). Importantly, it has been demonstrated that execution of motor tasks induces lasting changes in cortical activity that can be meaningfully compared across experimental conditions to infer differences in motor control (Eidelberg, 2009). We expected to find differences between PD patients and healthy controls in the neural after-effects of self-paced and cued movement, possibly as a function of the movement conditions used.

IV.2 METHODS

SUBJECTS

Twenty PD patients (PD, five female), recruited from the outpatient clinic of VU University medical center, and fifteen healthy age-matched controls (CO, three female) participated in the experiment. PD patients were 62.3 $\pm$ 2.5 (mean $\pm$ SD) years of age (CO 63.2 $\pm$ 7.9 years), had a Mini Mental State Examination (MMSE) of 29.2 $\pm$ 1.5 (CO 29.5 $\pm$ 0.6), Hoehn and Yahr stage (HY) range 1.5-3, UPDRS range 22-71, and disease duration of 6.3 $\pm$ 3.5 years. The study was approved by the Medical Ethics Committee of VU University medical centre. Subjects signed an informed consent form before participation. All patients were on a stable medication regimen and tested in the ON-phase 1.5 hours after their last medication-intake to minimize motion artifacts during the MEG recordings; more details about the patients can be found in Table IV.1 in Section IV.8. All participants were right-handed.

PROCEDURE

Lying supine with eyes open, subjects rhythmically squeezed an air-filled rubber bulb.[1] The pace for this task was set by an 80 bpm sensory stimulation delivered by an expandable membrane attached to the ventral side of the left index finger. Somatosensory stimulation was chosen because it is equally effective for cueing in PD as auditory stimulation (Nieuwboer et al., 2007) but may also be used in future fMRI experiments aimed at gathering essential complementary information to the present study. Subjects received written instructions about conditions that were projected onto the ceiling.

The experiment consisted of cued and self-paced conditions, i.e. conditions with continuous sensory pacing with which subjects had to synchronize, and conditions with a brief initial period prescribing the rhythm followed by self-paced force production continuing this rhythm (Figure IV.1). In both conditions, two types of cueing were used, one with regular inter-stimulus intervals (750 ms, i.e. 80 bpm) and one with irregular intervals (mean = 750 ms, SD = 25 ms). The jitter was large enough to be salient, but not so large that the task would become a tracking/reaction task. The cued conditions (RC: regular, and IC: irregular) started with 180 s of rest followed by three 30-s movement periods consisting of

[1] No force level was prescribed and subjects were free to exert any amount of force during the tasks.

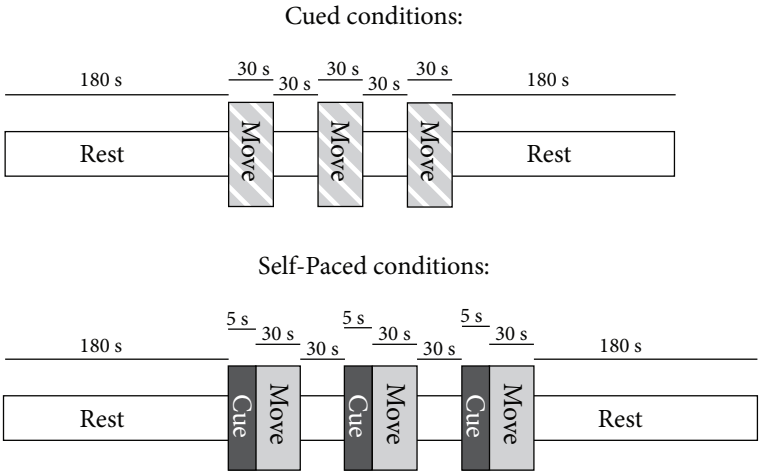

Figure IV.1: Experimental conditions. Two external cueing with either regular or irregular cues (RC and IC, respectively; upper panel), and two self-paced conditions (SP) with 5-s regular or irregular lead-in (the latter is not reported here).

cued movement (squeezing the bulb) separated by two 30-s rest periods, and concluded by another 180 s of rest. In the self-paced conditions the 30-s movement periods were replaced by a 5-s cueing period followed by 30 s of self-paced movements (SP).[2] The motor task was designed such that the motor demands were modest, ensuring that differences in neural activity would not be caused by differences in motor performance between PD patients and controls.

Each condition was presented once for a total measurement time of 34.5 min. The order of the conditions was counterbalanced over subjects for both PD and CO.

DATA ACQUISITION AND PREPROCESSING

Brain activity was recorded using a 151-channel whole-head MEG system (CTF Systems Inc., Vancouver, Canada) using 3rd order synthetic gradiometers. Pressure from the air-filled bulb was recorded simultaneously using a custom-built pressure sensor. All signals were low-pass filtered at 200 Hz prior to digitization at a rate of 625 Hz. Peaks in the

[2] As the outcome of RC and IC self-paced conditions largely agreed, we restrict their report to the RC self-paced condition abbreviated as SP.

pressure signals were determined after applying a 2nd order bi-directional Butterworth filter around the pacing frequency (0.3 to 2.4 Hz). Signals were preprocessed using CTF Systems Inc. software and analyzed using Matlab (The Mathworks Inc., Natick, MA).

A subject's data were discarded if there were too many artifacts (e.g. eye movements; included CO: 14, PD: 16 subjects). For each subject and condition there were three movement periods. Pressure signals were excluded per movement period if the number of movements did not match the number of stimuli in the last 25 s of each movement period, or if there was no continuous movement in the last 25 s of each movement period (included CO: RC 35, IC 19, SP 40 (out of 42); PD: RC 38, IC 28, SP 36 (out of 48) movement periods). MEG signals were excluded per condition if subjects continued the task during rest or if the pacing was not followed during one or more of the three movement periods (included CO: RC 14, IC 13, SP 13 (out of 14); PD: RC 15, IC 14, SP 14 (out of 16) subjects).

IV.3 DATA ANALYSIS

The total synchrony error, defined as the sum of the absolute difference between moments of maximal pressure and stimulus times, served as performance measure for the cued conditions. In the SP condition performance was assessed via the mean movement frequency and the inter-response variability. The initial 5 s were omitted to exclude transient behavior.

Bilateral M1s were localized using synthetic aperture magnetometry (SAM) beamformers (Vrba and Robinson, 2001) contrasting MEG activity during rest and movement (see Section IV.8). Average sources are shown in Figure IV.2 and referred to as left and right M1, even though the identified sources may involve motor related areas other than the sole primary ones (e.g. pre-motor). No focal sources could be identified in the alpha band.

We assessed $M1_{left/right}$ activities via the source signals' power in different time-windows within distinct frequency bands. Time-frequency-dependent power was estimated via the Hilbert amplitude after filtering in alpha (7-11 Hz) and beta (13-30 Hz) bands using a 3rd order bi-directional Butterworth filter (Figure IV.3).

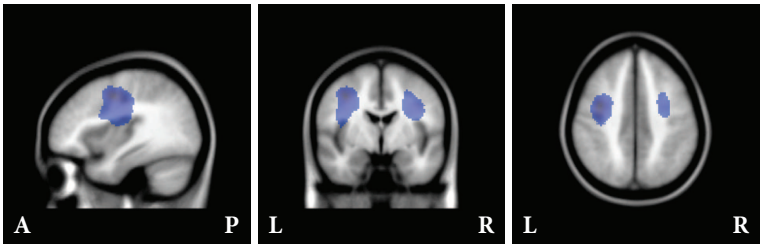

Figure IV.2: SAM sources in bilateral M1. Significance of voxel pseudo-*t* values was determined using a permutation test (Nichols and Holmes, 2002). Peaks in mean power differences (moving vs. rest) fell within voxels that were significantly different in power between rest and movement.

The filtered source signals were normalized by dividing through their standard deviation during 120 s of the pre-movement rest period. We used the aforementioned 20-s time-windows centered within each 30-s movement period and averaged the spectral power to determine *movement-related* power levels. These outcomes were evaluated statistically for each frequency band to assess the adaptation of power over movement periods. Further, we tested for effects in the post-movement period by computing the mean beta power over a 5-s interval of rest 2 s after the final movement period; the 2-s time gap guaranteed that subjects had stopped all movement. In view of Figure IV.3 (lower panel), we also investigated longer, sustained post-movement changes in the alpha band by using a 30-s interval starting 40 s after movement termination. This interval was determined by averaging the post-movement data over 5-s intervals and by finding the values that were significantly larger than the pre-movement resting level as determined by paired *t*-tests.

STATISTICS

The total synchrony error was evaluated across conditions using a 2-way mixed design ANOVA (between-subject variable *group*, PD or CO, and within-subjects variable *cueing*, RC or IC). Mean frequency and inter-response variability were investigated using two-sample *t*-tests, and for the activity during the three movement periods we used a $2\times3\times2\times3$ mixed design ANOVA (between-subject variable *group*, within-subjects variables *period*, 1, 2, or 3, *hemisphere*, $M1_{left}$ and $M1_{right}$, and *cueing*) for each frequency band separately. Movement-related power might generally depend on the amount of force produced. Hence we investigated the force levels for the three movement periods with a $2\times3\times3$ mixed

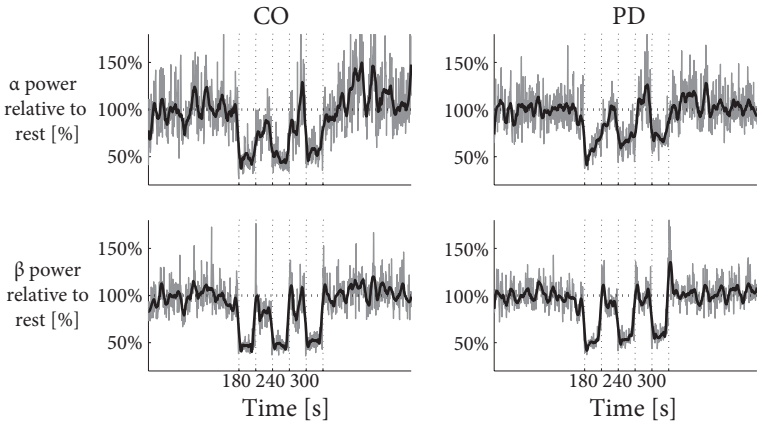

Figure IV.3: Task-related changes of spectral power in alpha and beta bands relative to rest averaged over subjects and cued conditions for the CO and PD group. Gray lines represent 'raw' power changes (black lines are low-pass filtered versions to improve legibility).

design ANOVA (*group*, *period*, and *cueing*). Pre- and post-movement resting state M1 power (for beta in the 5-s and for alpha in the 30-s interval) was compared using a $2\times2\times3$ mixed design ANOVA (*group*, *hemisphere*, and *cueing*). We applied the Huynh-Feldt correction whenever the assumption of sphericity was violated. A significance level of $\alpha = 0.05$ was adopted. Error bars in all figures represent standard errors of the mean.

IV.4 RESULTS

MOTOR PERFORMANCE

Figure IV.4 suggests that the total synchrony error in the IC condition was higher than in the RC condition, which was confirmed statistically ($F_{1,15} = 42.8, p < 0.001$). As expected, performance did not differ significantly between CO and PD across conditions.

The force level decreased significantly with increasing *period* ($F_{1,22,19.54} = 12.81, p = 0.01$); see Figure IV.5. This effect matched the influence of period for the alpha and beta bands: larger forces were accompanied by lower alpha and beta power levels. There was also an influence of *cueing* ($F_{2,32} = 5.10, p = 0.012$), indicating that force levels in the SP conditions were larger than in the RC and IC conditions (although only significantly for the latter).

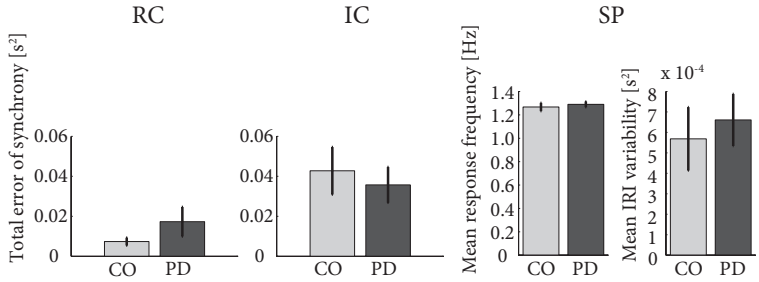

Figure IV.4: Left, middle panels: performance in the RC and IC conditions as measured by the total synchrony error. Right panel: mean movement frequency and inter-response variability in the SP condition.

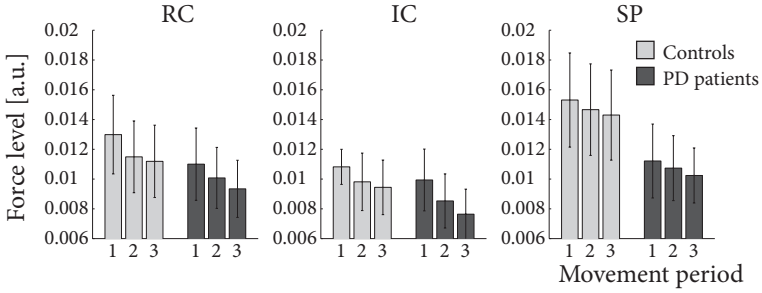

Figure IV.5: Force levels for each group and condition. Force level decreased with movement period. Also, force levels in the SP condition were larger than in the IC condition.

MOVEMENT-RELATED M1 ACTIVITY

In analyzing movement-related M1 activity (Figure IV.6) we found that alpha and beta power increased significantly with movement *period* ($F_{2,46} = 26.43, p < 0.001$ and $F_{2,46} = 18.78, p < 0.001$, respectively). A significant influence of *hemisphere* ($F_{1,23} = 10.54, p = 0.004$) was found for the beta power, which was on average higher in $M1_{right}$ than in $M1_{left}$, i.e. contralateral to the movement. There was also a main effect of *cueing* ($F_{2,46} = 3.26, p = 0.048$), as power levels for the SP condition deviated less from baseline than in the RC and IC conditions.

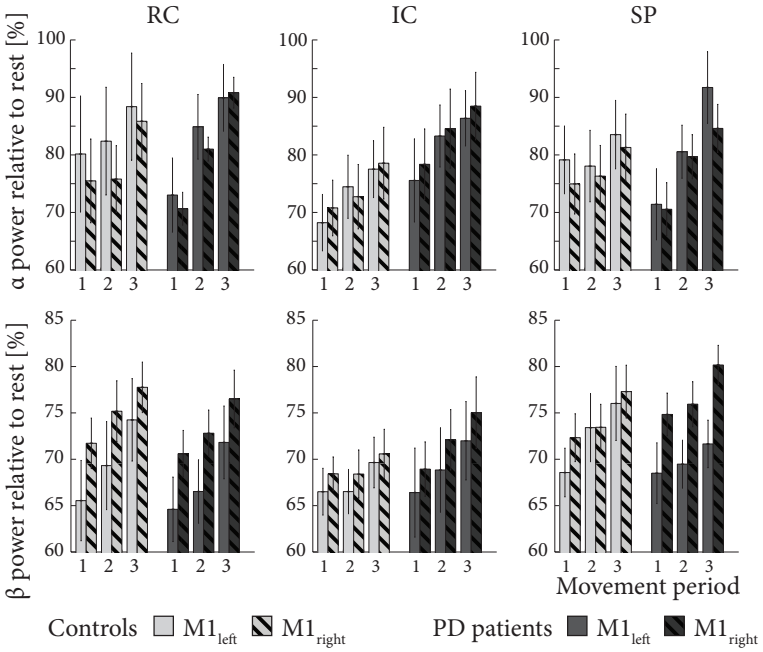

Figure IV.6: Source power during the three movement periods for the alpha and beta frequency bands for $M1_{left}$ and $M1_{right}$. Power increased with movement period. In the beta band, the right hemisphere displayed higher power levels than the left.

PRE-POST-MOVEMENT COMPARISON

The differences between pre- and post-movement beta power (Figure IV.7) revealed a significant main effect of *hemisphere* ($F_{1,23} = 20.69, p < 0.001$) and a significant *cueing* $\times$ *hemisphere* interaction ($F_{2,46} = 4.20, p = 0.021$). Note that we tested for dependencies between this after-effect and power during the (last) movement period but found no significant correlation, i.e. the differential after-effects were not caused by differences in movement-related activity between conditions.

The alpha band also revealed a change in the 5-s post-movement period (Figure IV.3), but this change was similar in consistency and size to the background variability during pre-movement rest. However, we found a consistent and large increase in alpha power from baseline level, starting approximately 40 s after movement termination and lasting

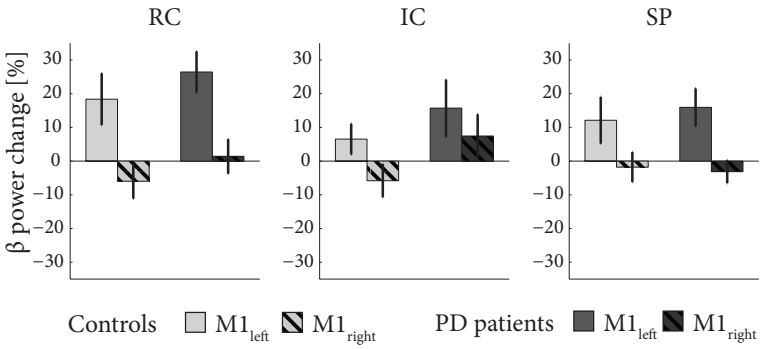

Figure IV.7: Power changes between pre- and post-movement resting state activity for the beta band. RC and SP conditions resulted in larger (positive) changes in $M1_{left}$ compared to (negative) changes in $M1_{right}$. This difference was absent in the IC condition.

for 30 s. As shown in Figure IV.8, there was a significant effect of *group*, as increases were large for CO but not for PD; $F_{1,23} = 12.68, p = 0.044$.

To examine the sustained change in alpha activity in greater detail we finally performed a principal component analysis of the surface patterns and found a fairly homogeneous distribution of (baseline corrected) alpha activity that increased primarily in more frontal channels. These results are detailed in Section IV.8.

IV.5 DISCUSSION

In the present study, we used MEG to examine effects of external cues on bilateral M1 activity during rhythmic movements. M1 activity during movement was strongly related to the exerted force level: the influence of movement period clearly matched differences in force level. In the salient post-movement changes of neural activity we identified a recovery period of 5 s after movement termination, signified by an increase in beta power that differed between the three movement conditions, but not between groups. We also found a large increase in alpha power starting approximately 40 s post-movement, which lasted about half a minute. Interestingly, this change in alpha activity did discriminate between groups as it was present in controls in the cued conditions, but not in PD and in conditions without cueing.

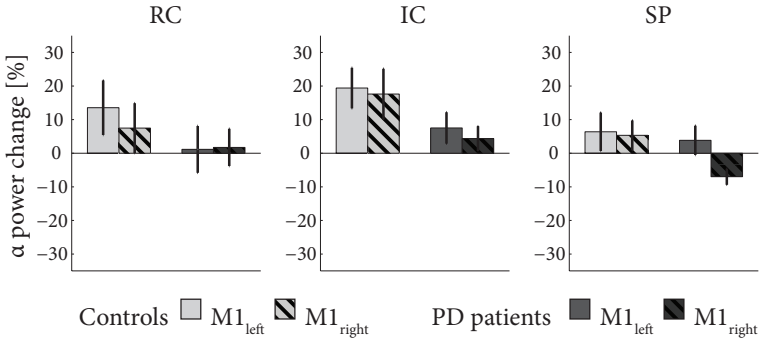

Figure IV.8: Changes in power between pre- and post-movement resting state activity for the alpha band focusing on the 30-s period starting 40 s after movement termination. There was only and increase for the controls.

The increase in beta power in the post-movement period supports the interpretation that beta oscillations signify an idling motor cortex. The duration of this beta rebound, however, differed from more conventional event-related synchronization, which is usually considered indicative of movement termination (Pfurtscheller et al., 1998; van Burik et al., 1998) and typically lasts only a few hundred milliseconds. The presently observed 5-s duration and bilateral distribution of the beta effect supports the suggestion of Cassim et al. (2001) that post-movement beta synchronization reflects an active inhibition of M1 via somatosensory afferents. This may also explain why regular cueing led to the steadiest performance in both PD patients and controls and required the strongest post-processing: regular cues are predictable and afford falling into the 'groove', whereas irregular cues must be dealt with one at a time. The behavioral switch involved in terminating a steady, regular performance might be more demanding than terminating a performance guided by irregular cues. No group differences were found in the beta band. Given the interconnectedness of basal ganglia and motor cortex, dopamine depletion in the striatum may well have ramifications to the motor areas. Previous research did report effects of PD on M1 activity, but mostly via event-related analyses (Pfurtscheller et al., 1998) with patients in the OFF-phase (Fattapposta et al., 2000). By investigating patients in the ON-phase we ensured that the observed effects were not just epiphenomenal to deteriorated performance. The adopted design, however, led to sustained effects on the neural activity of the motor areas at rest that, apparently, were too subtle to differentiate between controls and mid-stage PD.

The interpretation of increasing alpha power is less straightforward. Short-term alpha synchronization may signify deactivation of cortical areas, with the enhanced mu rhythm in M1 during visual processing (Pfurtscheller et al., 1996) as a case in point. In our experiments, however, subjects did not have to process any visual input during rest. Of course we cannot exclude some incidental visual processing, but we deem it highly unlikely that it lasted for 30 s, was only present post-movement, and would differ significantly between groups. Decisively, however, the increase in alpha power started as late as 40 s after the last movement, and thus cannot be attributed to a mere 'overshoot' of the mu rhythm in vacant neural populations.

Although our results are descriptive in nature, we submit that the delayed and sustained change in alpha power in the healthy subjects reflects a gradual loss of focus after finalizing the motor task. Subsequent analysis of the corresponding spatial distribution of activity revealed a very broad and quite homogeneous pattern and increases during post-movement resting states occurred predominantly in frontal regions. These change resembled that of a fatigue-induced anterior shift of alpha power (Section IV.8), which has been interpreted as a change in central processing of afferent sensory input (Boonstra et al., 2005). Interestingly, only healthy controls showed the increase in alpha power, especially after cued performance (see Figure IV.8), suggesting a return to a relaxed, non-focused state. As both groups performed the same trials, it is unlikely that the controls were more fatigued than the PD patients. The increase is better explained by the motor perseverance phenomenon (Ebersbach et al., 1994), emanating from a 'lingering' in the state induced by the cued performance, with increased levels of attentional activity, in line with suggestions that PD patients have problems with shifting behavior, and rely much more on external cues during performance (Hallett, 2008; Ebersbach et al., 1994; Georgiou et al., 1994; Hayes et al., 1998; Stolwyk et al., 2005). Furthermore, since motor perseveration has been observed in early stage non-demented PD patients (Stoffers et al., 2001) it may well have prevented the long-lasting increase in resting state alpha power observed in the controls.

IV.6 CONCLUSIONS

As cortical M1 activity during movement episodes was similar in patients and controls irrespective of presence and type of cue, we conclude that cortical activity during motor performance as such does not explain why cues are so effective in improving rhythmic movements. Interestingly we found post-movement activity that persisted much longer than previously reported in the literature. For the beta band, this activity lasted up to 5 s after movement termination, reflecting a motor recovery period. This observation was similar for PD patients and controls, whereas effects in the alpha band differed significantly between groups. To explain this finding, we suggest that long-lasting motor perseveration, known to be present even during early stages of PD, is associated with the absence of the post-movement increase in power that is normally found in controls.

IV.7 ACKNOWLEDGMENTS

This work was financially supported by the Netherlands Organisation for Scientific Research (NWO grant #452-04-344 awarded to A.D.) and the Internationaal Parkinsonfonds and the van Leersumfonds (grant #IPF-2006-1 and #AFD/ML/2903 awarded to E.v.W.). We thank Floor Buma for her assistance in collecting the MEG data.

IV.8 SUPPLEMENTARY MATERIAL

PATIENT INFORMATION

Additional patient information is provided in Table IV.1.

LOCALIZATION OF LEFT AND RIGHT M1 USING SAM BEAMFORMERS

Left and right M1 ($M1_{left/right}$) were determined using synthetic aperture magnetometry (SAM) beamformers (Vrba and Robinson, 2001). We used an averaged MRI onto which to project the sources (Mazziotta et al., 1995), as this readily allows for a statistical evaluation (Nichols and Holmes, 2002) of the motor-related activity across subjects. To determine the task-relevant areas we compared beta band power (13-30 Hz) during 3×20 s of movement

Table IV.1: Sex, age, dominant side of PD (DS), Hoehn-Yahr scale (HY), MMSE, and UPDRS total score as measured in the ON state, occurrence of freezing, and medication.

No.	Sex	Age	DS	HY	MMSE	$UPDRS_{total}$	Fr.	Medication
1	m	63	R	2.5	30	35	N	L-Dopa 375mg/ ropinirole 24 mg
2	m	82	L	3.0	29	71	N	L-Dopa 500 mg
3	f	54	L	2.0	30	22	N	L-Dopa 500 mg/pergolide 2 mg
4	f	62	L	2.0	30	38	N	selegiline 5 mg
5	m	76	R	3.0	27	25	Y	L-dopa 1500 mg/pramipexol 0.8 mg
6	m	63	R	3.0	29	26	Y	L-Dopa 625 mg
7	f	53	L	3.0	24	37	Y	L-Dopa 500 mg/pergolide 1 mg
8	m	74	R	3.0	30	62	Y	selegiline 10 mg/pramipexol 1,5 mg
9	m	76	L	3.0	30	62	N	L-Dopa 500mg
10	m	56	R	2.5	30	38	Y	L-Dopa 330 mg/ropinirole 18 mg mg
11	m	50	R	1.5	28	24	N	L-Dopa 375mg/pramipexol 2,1 mg
12	m	27	L	2.5	30	58	N	selegiline 5 mg
13	m	59	L	2.0	30	44	N	pramipexol 1,32 mg
14	m	59	L	2.5	28	47	Y	L-Dopa 375mg/ ropinirole 15 mg
15	f	76	L	3.0	30	40	Y	L-Dopa 187,5mg/ ropinirole 15 mg
16	m	63	R	2.5	29	71	Y	L-Dopa 1225 mg/pergolide 4mg
17	m	65	R	3.0	30	58	Y	L-Dopa 625 mg/pergolide 5 mg
18	m	63	L	3.0	30	56	Y	L-Dopa 1000 mg/pramipexol 2,8mg
19	m	74	L	2.5	29	50	Y	L-Dopa 625 mg
20	f	50	R	2.0	30	23	N	L-Dopa 625 mg/pergolide 1 mg

with 3×20 s of rest (each 20-s interval was centered in the corresponding 30-s block to avoid transients; see Figure IV.1 for every voxel and subject). The resulting pseudo-t values were averaged over subjects for each group and condition yielding maximal significant contrasts in the bilateral M1s (see Figure IV.2). MEG data were projected onto these sources yielding the time-dependent activity in $M1_{left/right}$.

PRINCIPAL COMPONENT ANALYSIS OF THE ALPHA POWER

We analyzed the topography of alpha activity using principal component analysis (PCA) as described in (Vrba and Robinson, 2001). Equivalent to the time series analysis of the beamformer source, we first computed the alpha power at all 151 MEG channels. For each condition and group, power values were averaged over subjects yielding $N = 151$ signals $\alpha_1, \alpha_2, \ldots, \alpha_N$ as functions of time. These signals were mean centered and normalized

to unit variance resulting in $x(k) = (\alpha_k - \bar{\alpha}_k)/\sqrt{\text{var}(\alpha_k)}$; $\bar{\alpha}_k$ and $\text{var}(\alpha_k)$ respectively denote the mean and variance of α_k over time. Using these time series, we computed the covariance-matrix with elements $C_{ki} = \text{Cov}(x_k, x_i)$ prior to singular value decomposition. Throughout conditions and groups this led to two primary modes that covered about 80% of the signals' variance as illustrated in Figure IV.9. The first mode's topography was quite homogenous and its time evolution mimicked the experimental protocol (initial resting state, three 30 s blocks force production, final resting state). The second mode did not clearly correlate with the experimental protocol but hinted at an anterior-posterior modification of the alpha power distribution, predominantly in frontal challenge.

To zoom in on the more sustained increase in alpha activity post movement, we repeated these analyses after discarding the movement periods of the time series. That is, we only included the pre- and post-movement resting states, for which individual PCAs were performed.

As summarized in Figure IV.10, in all conditions and groups, the primary modes covered about 50% of the data variance for both the pre- and post-movement period (the remaining variance was homogeneously spread over all higher modes; not shown). Interestingly, the difference between these initial modes displayed a redistribution of alpha power post movement by means of an increase in frontal and a decrease in parietal and occipital channels (lower middle panels in Figure IV.10). This pattern was most prominent in the control group in the RC condition and in the PD group in both RC and IC conditions, in line with the main results shown in Figure IV.8.

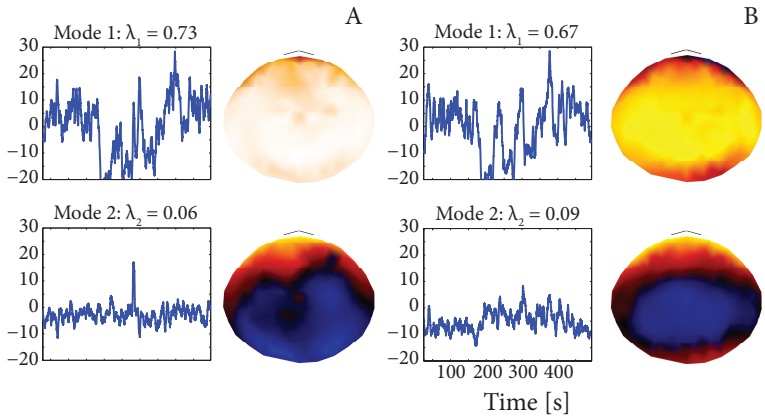

Figure IV.9: PCA results for the IC condition in the CO group (panel A) and in the PD group (panel B).

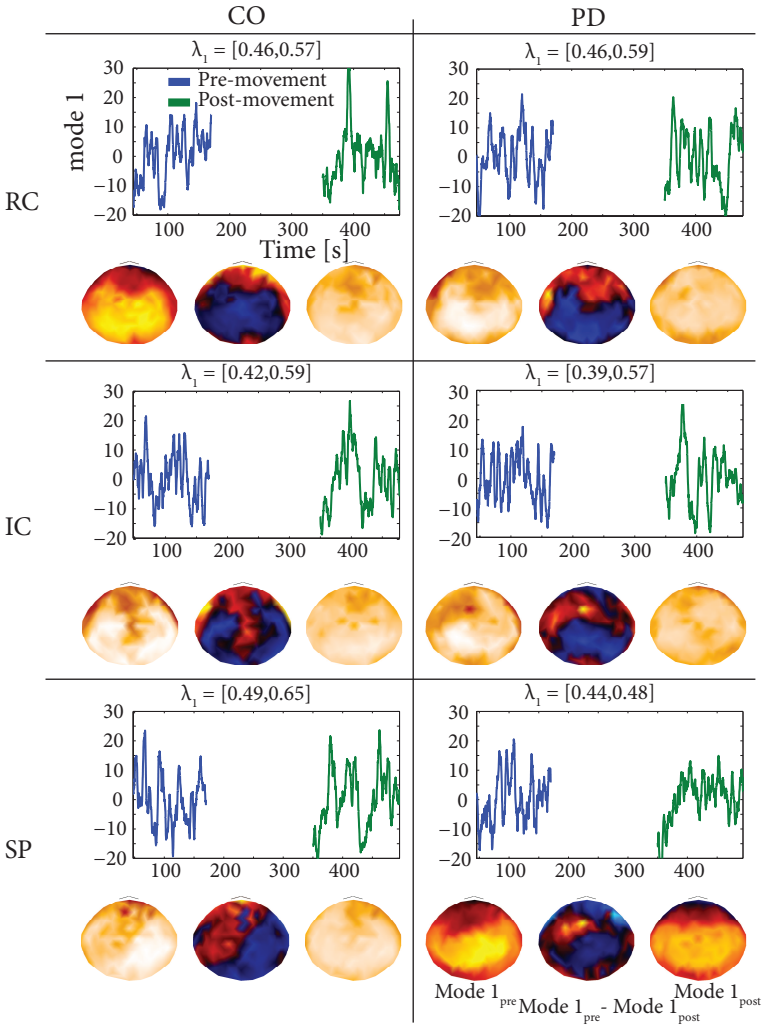

Figure IV.10: Differences between the primary principal components (PCA mode1) pre and post movement. Top panel: projected time series, lower left/right panels: PCA modes; middle panel: difference between modes.

CHAPTER V

SLOWING OF M1 ACTIVITY IN PARKINSON'S DISEASE DURING REST AND MOVEMENT – AN MEG STUDY

Abstract

Parkinson's disease is characterized by motor and cognitive problems that are accompanied by slowing of neural activity. This study examined the relationship between neural slowing and disease severity during rest and motor performance. Primary motor activity was assessed by means of magnetoencephalography during rest and rhythmic movements. Motor output and event-related cortical power in the alpha and beta frequency bands were determined. UPDRS total and subscores were used to pinpoint correlates of neural slowing (change of power towards lower frequencies) during both resting state and the production of rhythmic movements. By design, motor performance was similar for both the patients and the controls. PD patients showed slowing of neural activity which increased with disease severity. Slowing during rest showed the clearest correlation with cognitive UPDRS subscores, whereas slowing during movement correlated best with the motor UPDRS subscore. These results suggest that slowing is functionally modulated and that different mechanisms are responsible for neural slowing during rest versus movement. Neural slowing must be viewed in a broader context than previously thought because it is not solely related to impaired motor performance but also to impaired cognition.

Adapted from:

A. N. Vardy, E. E. H. van Wegen, G. Kwakkel, H. W. Berendse, P. J. Beek, and A. Daffertshofer, Slowing of M1 activity in Parkinson's disease during rest and movement – an MEG study. *Under review*.

V.1 INTRODUCTION

Parkinson's disease (PD) is accompanied by changes in neural activity, most notably in oscillatory activity in various cortical and subcortical areas (Berendse and Stam, 2007; Brown, 2007; Schnitzler and Gross, 2005). Oscillatory activity in general and synchronization of neuronal activity in particular reflect a variety of motor and cognitive processes. Are changes in oscillatory activity generic correlates of the disease, or are they modulated by tasks and/or by disease severity? Put differently, if synchrony is altered, which functions are affected most? One such change in oscillatory activity that has raised considerable interest in relation to PD is the slowing of neural activity, where spectral power shifts to lower frequencies (Stoffers et al., 2007; Moazami-Goudarzi et al., 2008; Bosboom et al., 2006; Soikkeli et al., 1991; Salenius et al., 2002; Stanzione et al., 1996). Stoffers et al. (2007) showed that during resting state magnetoencephalographic (MEG) recordings in early stage, untreated PD patients, cortical activity exhibited higher relative power in the alpha (and theta) band and lower relative power in the beta (and gamma) band compared to controls. This slowing of neural activity in the cortex in PD can be particularly important through the extensive connectivity between the cortex and subcortical areas including the basal ganglia (Moazami-Goudarzi et al., 2008; Soikkeli et al., 1991; Brown, 2003). And, in view of the complex symptomatology of PD, however, it is likely that the spectral changes are not limited to the resting state default network.

PD is commonly known for its characteristic motor problems such as freezing and shuffling gait, more general rigidity, tremor, and bradykinesia. It may therefore be hypothesized that changes in neural activity found during resting state can also be found during movement. Interestingly, Moazami-Goudarzi et al. (2008) localized a PD-related low-frequency power increase (in the lower alpha frequency band) in broad and bilateral fronto-insulo-temporal areas during resting state, suggesting an involvement of paralimbic and associative domains in the pathogenesis of PD. They postulated a persistent and deleterious increase in resting state activity in PD and proposed that the low frequency activation relates to the appearance of motor negative symptoms (like akinesia).

PD patients show movement-related problems originating from a disturbed functioning of the neural circuitry between thalamus, basal ganglia, and primary motor cortices that is associated with a reduction of dopaminergic cells in the substantia nigra (DeLong and

Wichmann, 2007). We therefore investigated whether the aforementioned slowing of neural activity in resting state extends to movement-related activation. We expected a similar but more pronounced slowing during movement, as proper motor functioning requires coordinated oscillatory activity, or changes thereof (Houweling et al., 2010a). We further investigated to what extent such slowing during the production of externally cued rhythmic movements is related to disease severity. We also performed the analysis during resting state to verify if our methods yield similar results regarding slowing of neural activity as reported in literature (Stoffers et al., 2007). We used three rhythmic motor tasks, adapted from cueing therapy, which is commonly employed in PD and entails the use of cues to guide rhythmic movements (Lim et al., 2005b; Nieuwboer et al., 2007; van Wegen et al., 2006). The movement tasks used were still easy enough to perform by both PD patients and healthy individuals, thereby ensuring that differences on a neural level are not attributable to differences in performance, but solely to the underlying pathology. The effect of disease severity was investigated against the background of the Unified Parkinson's Disease Rating Scale (UPDRS), in particular the mental and motor subscores, to pinpoint which facet of PD is related to slowing of neural activity.

V.2 METHODS

SUBJECTS

Eleven patients with Parkinson's disease (PD, three female) and eleven healthy age-matched controls (CO, three female) with artifact-free MEG and co-registered MRI were included in this study. PD patients were recruited from the outpatient clinic for movement disorders of VU University medical center. Some of the patients had participated previously in the RESCUE project (Nieuwboer et al., 2007). PD patients were 61.0 $\pm$ 15.5 (mean $\pm$ SD) years of age (CO 62.2 $\pm$ 8.35 years), had a Mini Mental State Examination (MMSE) score of 28.9 $\pm$ 1.8 (CO 29.5 $\pm$ 0.7), Hoehn and Yahr stage (HY) range 1.5-3.0, UPDRS-ON range 22-71, and disease duration of 5.1 $\pm$ 3.3 years. All patients were on a stable medication regimen and tested in the ON-phase approximately 1.5 hours after their last medication-intake; more details about the patients can be found in Table V.3 in Section V.8. All participants were right-handed. The study was approved by the Medical Ethics Committee of VU University medical centre. Subjects signed an informed consent form prior to participation.

PROCEDURE

Subjects were asked to perform a rhythmic motor task with their right hand, which consisted of rhythmically squeezing an air-filled rubber bulb while lying supine with eyes open. No force level was prescribed and subjects were free to exert any amount of force during the tasks. The tempo of performance was set by an 80 bpm sensory stimulation delivered by an expandable membrane attached to the ventral side of the left index finger (200 ms pulse duration, pressure 200 kPa). Subjects received visual written instructions about conditions via a computer display on the ceiling of the magnetically shielded room housing the MEG.

The experiment consisted of different movement scenarios: paced and self-paced conditions, i.e. conditions with sensory stimulation with which subjects had to synchronize continuously, and conditions with a brief initial cueing period prescribing the pace continued by self-paced force production (see Figure V.1). Two types of pacing were used, one with regular inter-stimulus intervals (750 ms, i.e. 80 bpm; regular cueing RC) and one with irregular, jittered stimuli (mean inter-stimulus interval = 750 ms, SD = 25 ms; irregular cueing IC). The paced conditions started with 180 s of rest followed by three 30-s movement periods consisting of cued movements (squeezing the bulb) separated by two 30-s rest periods, and concluded by another 180 s of rest. In the self-paced (SP) conditions the 30-s movement periods were replaced by a 5-s pacing period followed by 30 s self-paced movements. We restrict their report to the RC self-paced condition abbreviated as SP. The cortical activity in the rest periods was analyzed in Chapter IV, which revealed distinct changes in the post movement intervals – see also Section V.5. In view of these earlier analyses we focused here specifically on the three movement periods.

DATA ACQUISITION AND PREPROCESSING

Cortical activity was recorded using a 151-channel whole-head MEG system using 3rd order synthetic gradiometers (CTF Systems Inc., Vancouver, Canada). Pressure from the air-filled bulb was recorded simultaneously using a custom-built pressure sensor. Electromyograms (EMG) were recorded from the right flexors (*m. flexor carpi radialis*). All signals were low-pass filtered at 200 Hz prior to digitization at a rate of 625 Hz.

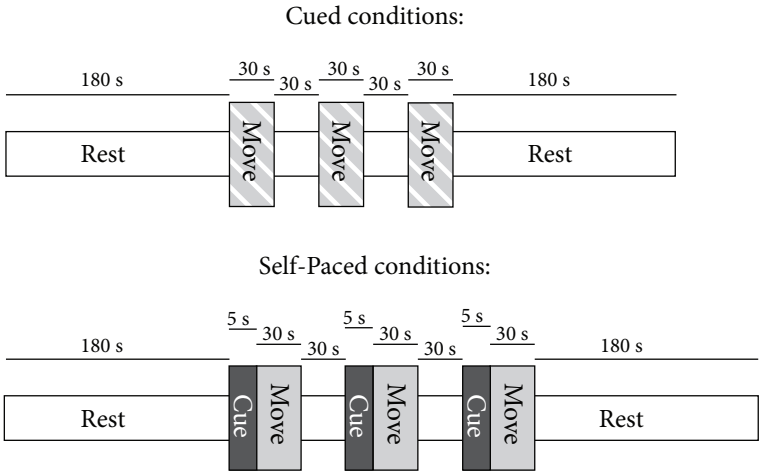

Figure V.1: Experimental design: subjects synchronized their movements in two paced conditions with either regular or irregular cues (RC and IC, respectively; upper panel), and two self-paced conditions (SP) preceded by either regular or irregular cues setting a rhythm that they had to continue (presented for 5 s); here we report only the SP condition with regular cues as lead-in. Each condition was presented once adding up to a total measurement time of 34.5 min. The order of the conditions was counterbalanced over subjects for both PD and CO.

MEG affords detailed recording of neural activity with a high temporal resolution. To investigate effects beyond those of ongoing activity and to increase the signal-to-noise ratio, we employed an event-related analysis which has been widely used to study, for example, attention (Golob et al., 2002), motor learning (Houweling et al., 2008), and changes in ERS/ERD cycles in PD (Pfurtscheller et al., 1998). Events were defined in relation to the peaks in the pressure signals. These peaks were determined by applying a 2^{nd} order bi-directional Butterworth band-pass filter around the 1.33 Hz pacing frequency (band 0.3 to 2.4 Hz). Signals were preprocessed using software provided by CTF Systems Inc. and analyzed using Matlab (The Mathworks Inc., Natick, MA).

A subject's data were discarded for a given movement period (there were three movement periods per condition, see Figure V.1), if it was impossible to detect peaks in the pressure signal. Subjects' data were discarded altogether if all movement periods failed to yield pressure peaks or if it was not possible to determine the left motor area (see Section V.3) (included subjects CO: 10, PD: 10).

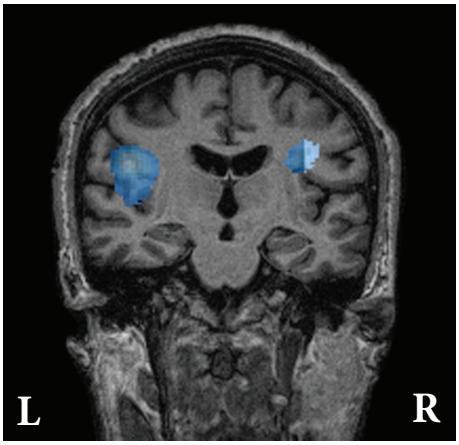

Figure V.2: Source $M1_{left}$ (and $M1_{right}$) in a representative control subject. For all but two subjects (one patient and one control), $M1_{left}$ could be determined successfully. See Section V.8 for details about the SAM beamformers in the beta band.

V.3 DATA ANALYSIS

We defined the degree to which the subjects performed the tasks correctly in terms of proper motor timing. When cueing was present (i.e. RC and IC conditions), a measure of synchronization error (the total error of synchrony) was employed, which was defined as the sum of the absolute difference between moments of peak pressure and stimulus presentation times. For SP, we determined the mean response frequency and the inter-response variability. The first 5 s of each of the three movement periods were omitted from the analysis to avoid transients. Force level was assessed by analyzing the pressure signals.

Using the MEG signals, we estimated sources via synthetic aperture magnetometry (SAM) beamformers (Vrba and Robinson, 2001) based on individual anatomical MR images; see Figure V.2 for an example and Section V.8 for details about methods. This determined the left primary motor cortex onto which MEG data were projected, yielding the time-dependent activity $M1_{left}$; we restricted analysis to the left hemisphere, i.e. contralateral to the force producing hand, as effects were most prominent in this hemisphere.

These activities were assessed further via the signals' *event-related field*, *power*, and *phase uniformity* (ERF, ERpow, and ERpu, respectively). For the ERFs, no statistically significant

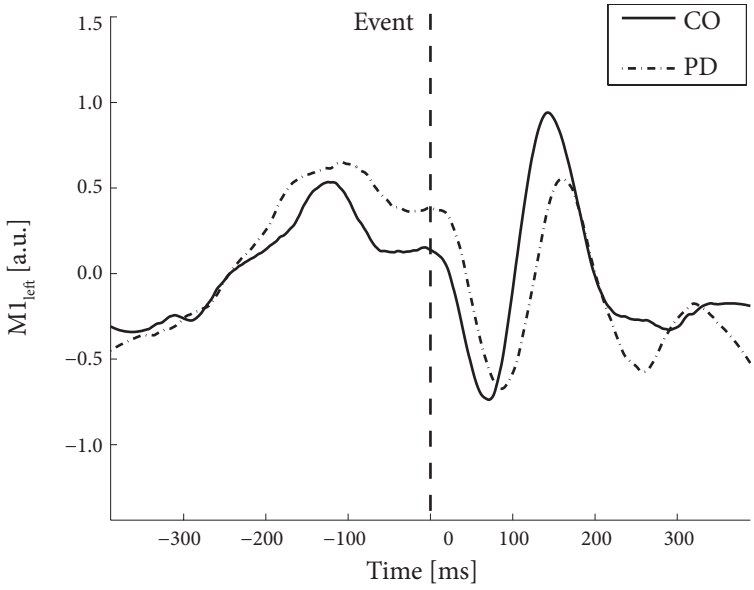

Figure V.3: ERFs of the left motor area ($M1_{left}$) in arbitrary units (a.u.) for PD and CO, averaged over conditions; Event = moment of peak pressure. There were no statistically significant differences between groups and between conditions. All fields revealed commonly found movement-related changes, in particular the well-known ERD-ERS-ERD complex (Pfurtscheller et al., 1998).

differences were found throughout subject groups and conditions and will therefore not be discussed further. For the sake of completeness, we illustrate the (grand) average ERF for the CO and PD groups in Figure V.3 and note that the differences shown were not statistically significant.

ERpow and ERpu were computed via the Hilbert transform of the source reconstructed data after filtering in 2Hz bands around frequencies $f = 7, 8, \ldots, 30$ Hz. This yielded time/frequency data spanning both the alpha (7-11 Hz) and beta (13-30 Hz) frequency bands. The three movement periods were analyzed whenever event-defining peaks were unambiguously detectable in the pressure signals. Signals were assessed in [-350, 350] ms epochs around all detected events of a trial (on average 60-90 events per trial). For the ERpow we averaged the power over events, for the ERpu we determined the phase coherence over events; see Section V.8 for details. Changes in event-related synchronization/ desynchronization (ERS/ERD) were determined through ERpow and ERpu as a function

of time (averaged over the above defined frequencies). The overall neural synchrony was assessed further by computing ERpow and ERpu as a function of frequency (averaged over the entire epoch). To anticipate, ERpow revealed significant differences between the two groups. These differences motivated the following analyses based on univariate data of individual subjects. First, we computed *relative power* as the fraction contributions of the alpha and beta band in ERpow and, second, the *median frequency* of the ERpow; both measures were also compared between groups (see below). Relative power and median frequency served to quantify slowing of neural activity. In order to investigate the relationship between disease severity and slowing, we finally correlated the two measures with the UPDRS scores of the PD patients. A similar analysis was performed on resting state data to confirm the slowing of neural activity found during resting state. These results are reported in Section V.8.

STATISTICS

Force levels were analyzed using the pressure signals which were averaged within subjects prior to assessing influences of *group* or *condition* using a 2×3 mixed design ANOVA (between-subject variable *group*; CO and PD, within-subjects variable *condition*; SP and RC, IC,). By contrast, ERpow and ERpu formed sets of time/frequency data, one for each subject in either the CO or PD group and for each condition. There, we analyzed the series using a principal component analysis (PCA) after either averaging over time or frequency. For each subject and for each condition, the time/frequency series served as multivariate input for the PCA. From this, the primary principal component (i.e. the mode accounting for the largest amount of variance) was determined to study effects of group and condition. If the primary principal component accounted for at least 75% of the total variance, then the coefficients of this component for each subject and condition were tested using an ANOVA using the same 2×3 mixed design as for the force levels. Relative power and median frequency were compared to the UPDRS scores (using linear regression to determine the significance of the regression coefficient) to evaluate their association with disease severity. Because the UPDRS score is aggregated over several parts, namely I: mental functioning, II: activities of daily life (ADL), and III: motor performance, we analyzed the contributions of each of the subscores using the same linear regression analysis.

A significance level of $\alpha = 0.05$ was used throughout the analysis. Error-bars in figures represent the standard error of the mean. Outliers were determined based on the mean

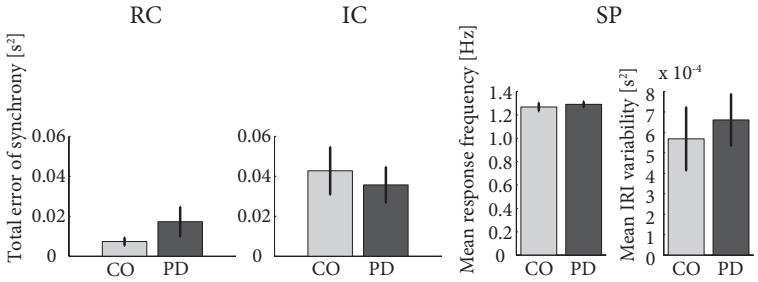

Figure V.4: Quality of performance (timing error) in the different conditions. There was no significant group difference implying that differences in neural activity between CO and PD could not be attributed to changes in motor performance during the experiment.

centered values for each variable separately. A time/frequency-series was defined as an outlier if it deviated more than two standard deviations from the mean for more than 10% of its length. This ensured that only traces which were not similar in shape were discarded as mean level was not important. We note that the coefficients of the primary principal component were tested, while the figures depict the group and/or condition averages.

V.4 RESULTS

MOTOR PERFORMANCE

Timing was found to be similar for all three conditions (see also Figure V.4) and movement tempo agreed between groups (see section V.8). The RC condition was performed slightly more accurately ($F_{1,15} = 42.8, p < 0.01$) than IC where force levels were also lower ($F_{2,30} = 10.84, p < 0.01$), although we did not instruct subjects to produce a specific force level. There were no differences between the two groups. Only two PD patients exhibited tremor during the recordings as determined by inspection of EMG recording of the right *m. flexor carpi radialis* (see section V.8).

EVENT-RELATED POWER

While the time-dependent ERpow did not reveal significant differences between groups or conditions, the PD patients displayed more power in the alpha band and less in the

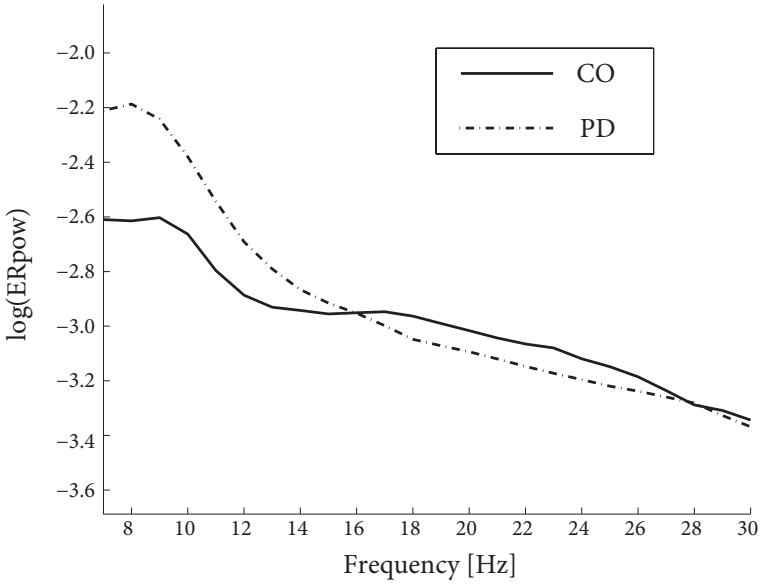

Figure V.5: Event-related power (ERpow) as function of frequency. There was a significant difference between the PD and CO groups for the ERpow traces, as PD patients showed less power in the beta band and more power in the alpha band. The primary mode of the PCA explained 93% of the total variance. There was no significant effect of cueing type.

beta band, implying a slowing of oscillatory activity as shown in the frequency-dependent ERpow in Figure V.5. This effect was confirmed statistically ($F_{1,12} = 6.870, p = 0.023$), where the primary principal component accounted for 93% of the total variance.

ERpow was further investigated through its median frequency that we compared between movement and resting state (median frequencies for each subject were averaged over conditions). As listed in Table V.1, the median frequency during resting state was higher than during movement and this difference was greater for the PD patients ($t_8 = -4.06, p < 0.01$) than for the controls ($t_9 = -2.37, p < 0.05$).

To analyze the shift in power as a function of disease severity, we computed the relative power as the fraction of power of the alpha band divided by that of the beta band. We then pooled the relative power over the three conditions yielding three averaged values for each subject. We found a significant influence of UPDRS score on the relative power

Table V.1: Comparison of median frequency between movement and resting state for the controls and the PD patients. For both groups the median frequency during movement was significantly lower than during resting state. The effect was greater for the PD patients.

	CO		PD	
	Movement	Resting state	Movement	Resting state
Median ± SD [Hz]	13.63 ± 1.78	14.85 ± 0.94	11.56 ± 0.99	13.98 ± 1.33
t_{df}, p	$t_9 = -2.37, p < 0.05$		$t_8 = -4.06, p < 0.01$	

($t_{23} = -3.42, p < 0.01$), where the alpha band contributed more and the beta band less to the total power for higher UPDRS scores (see Figure V.6). The median frequency also showed a lower value for higher UPDRS scores ($t_{23} = -2.41, p = 0.025$).

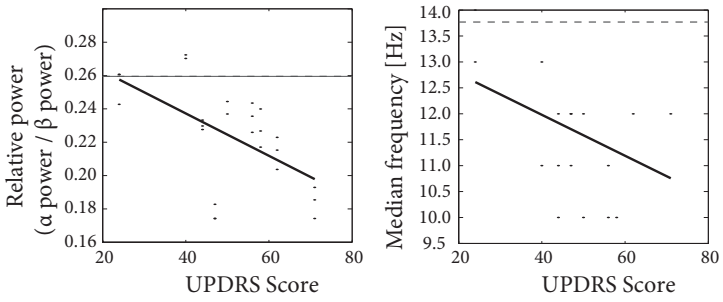

Figure V.6: Regression between neural slowing during movement and UPDRS scores. For both the relative power (left panel) and the median frequency (right panel) the PD patients revealed a slowing of neural activity when compared to controls (PD solid line versus CO dashed line). For PD there was a significant influence of UPDRS score on both relative power ($t_{23} = -3.42, p < 0.01$) and median frequency ($t_{23} = -2.41, p < 0.05$). The relative power and the median frequency of the PD patients differed significantly from those of the CO (a two-sample t-test revealed $t_{49} = -5.04, p < 0.001$; $t_{49} = -4.47, p < 0.01$ respectively).

Table V.2 summarizes the correlations between UPDRS total- and subscores and the slowing of neural activity as measured by the relative power and median frequency during movement and during resting state. Almost all UPDRS subscores showed a significant relationship with relative power during both movement and resting state; only the motor

subscore during resting state was not significant. For the median frequency, however, the distinction revealed a striking separation: the motor subscore had a very strong relationship with median frequency during movement, but not during resting state. Conversely, the ADL and mental subscores had a significant relationship with median frequency during resting state, but not during movement. Overall, this indicates a task-specific dependency of the UPDRS subscores on the slowing of neural activity.

Table V.2: Correlation strengths between slowing and UPDRS total- and subscores. Significant values are denoted in bold. The table shows the correlation coefficients, the t-test scores from the linear regression coefficient r, and probability values p. UPDRS scores during movement correlated with Relative power and Median frequency

UPDRS score correlations during *movement*

	Relative power			Median Frequency		
	r	t_{23}	p	r	t_{23}	p
UPDRS total	-0.5806	-3.4196	**0.0023**	-0.4483	-2.4053	**0.0246**
UPDRS mental	-0.4370	-2.3303	**0.0289**	-0.0630	-0.3025	0.7650
UPDRS ADL	-0.5524	-3.1777	**0.0042**	-0.0853	-0.4108	0.6851
UPDRS motor	-0.4584	-2.4737	**0.0212**	-0.5394	-3.0719	**0.0054**

UPDRS score correlations during *rest*

	Relative power			Median Frequency		
	r	t_{23}	p	r	t_{23}	p
UPDRS total	-0.5313	-3.0075	**0.0063**	-0.3915	-2.0402	0.0530
UPDRS mental	-0.5654	-3.2874	**0.0032**	-0.4288	-2.2763	**0.0325**
UPDRS ADL	-0.6298	-3.8885	**0.0007**	-0.4838	-2.6508	**0.0143**
UPDRS motor	-0.3689	-1.9032	0.0696	-0.2622	-1.3029	0.2055

EVENT-RELATED PHASE UNIFORMITY

For the ERpu, the primary principal component explained only 43% of the total variance offering insufficient statistical power for reliably interpreting further analyses. For the sake of completeness, we show the group averages for both the time- and frequency-dependent ERpu in Figure V.7.

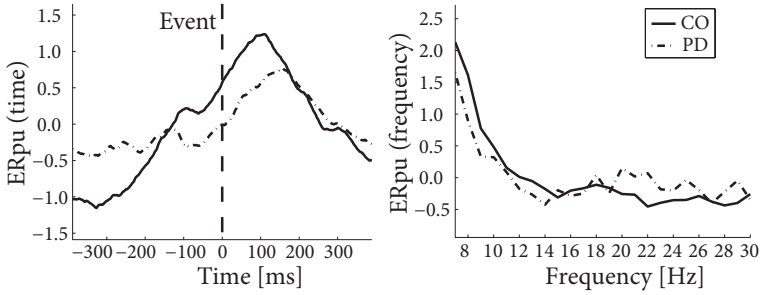

Figure V.7: Effect of group and condition on the event-related phase uniformity (ERpu); left panel: ERpu as a function of time, right panel: idem but as a function of frequency. There was a significant effect of *group* ($F_{1,15} = 11.27, p < 0.01$) and *condition* ($F_{2,30} = 3.49, p < 0.05$), but since the primary PCA mode explained only 43% of the total variance these results should be interpreted with caution.

V.5 DISCUSSION

We investigated the effects of PD on neural activity in the contralateral primary motor cortex. Previous studies reported a slowing of neural activity in conjunction with PD during rest (Stoffers et al., 2007; Moazami-Goudarzi et al., 2008; Bosboom et al., 2006; Soikkeli et al., 1991; Salenius et al., 2002; Stanzione et al., 1996). To date, it is unknown if this PD-related slowing is limited to the resting state or if it is also present during movement. To answer this we focused especially on motor performance, as movement impairment is one of the early signs of PD. Our motor tasks were designed such that PD patients and controls performed equally well, which enabled us to concentrate solely on the accompanying neural activity. Using the event-related analysis we found that PD patients exhibited more alpha and less beta power compared to healthy controls. That is, slowing of neural activity, in which cortical activity has higher relative power in the lower frequencies (alpha) and lower relative power in higher frequencies (beta), was clearly present in PD patients during both rest and motor activity. Remarkably, there was a clear correlation between the amount of slowing and disease severity as both decreasing relative power and median frequency were associated with increasing UPDRS scores. Stated differently, the more advanced the disease, the more pronounced was the slowing of neural activity in the primary motor cortex during motor performance. More details regarding resting state results are presented

in Section V.8. Taken together, our results indicate that slowing of neural activity is a structural, systemic – i.e. not only pertaining to the resting state – phenomenon in PD that progresses with the disease.

Only after analyzing the partial UPDRS subscores did the distinction between resting state and movement become apparent. The mental score correlated the least with the change in relative power during movement and the most during resting state. For the median frequency a similar distinction was found where the motor score was significantly correlated with neural slowing during movement, whereas the mental functioning and ADL scores were a significant correlate during resting state. This distinction indicates that slowing of neural activity is not just a general symptom of PD but that the slowing is task specific, or at least modulated by motor activity. Also, this difference in correlates during resting state and movement suggests that different mechanisms are responsible for slowing of neural activity in PD. A change in cortical power might be caused by abnormal activity in the subthalamic nucleus (Brown, 2003), a central hub that, when affected (and displaying neural slowing), can yield both cognitive and motor problems, as is the case in PD (Brown, 2007, 2006). That is, changes in cortical alpha and beta activity could be mediated by different (partly overlapping) networks that are more specific for motor tasks reflected by the UPDRS motor score or for cognitive aspects reflected by the UPDRS mental functioning and ADL scores. Note that changes in relative power can indeed be the result of an increase in alpha power, decrease in beta power, or a combination of both. Considering that the tasks used to determine the ADL score do require cognitive aspects like planning and coordination, unlike simple motor tasks, it is not surprising that the score for mental functioning and ADL show similar predictive properties.

Our analysis concentrated on the left motor cortex corresponding to the movement produced by the right hand. However, this does not imply that the here-reported effects are limited to this motor (output) area as M1 is densely connected to the basal ganglia, including the striatum. These deep brain regions are thought to be the origin of motor problems in PD (Brown and Williams, 2005; Hamani and Lozano, 2004; Krack et al., 1999). Changes in neural activity in the basal ganglia have adverse effects on the activity in the motor areas which may imply that our findings indeed represent secondary effects of the disease. Analysis of the basal ganglia using deep brain electrodes revealed profound changes in amplitude of activity and its distribution over different frequency bands (Brown, 2007,

2006). Over the years, deep brain stimulation in these regions has been used to improve motor-related problems in PD with considerable success (Benabid, 2003; Garcia et al., 2005; Goetz et al., 2005; Lozano et al., 2002; Samii et al., 2004). It is possible that this kind of stimulation also changes the power distribution of the motor areas, thereby counteracting the power shift found here and in previous studies focusing on the resting state. Future encephalographic studies should address this possibility in greater detail, and may also provide more insight into the links between deep brain power changes, shifts in frequency contents in the cortex, and disease severity.

The price we had to pay for studying patients that could perform the tasks equally well as healthy controls was that PD patients had to be in the ON-phase. Changes found in the spectral distributions may thus have been related to the intake of medication. The study of Stoffers et al. (2007) found a slowing of neural activity in the OFF-phase. In addition, when testing the effects of a dose of dopaminomimetics they found only slight changes in spectral power in areas other than the motor areas. We therefore conclude that medication was not responsible for the here observed slowing of neural activity. Conversely, it could have been the case that the medication attenuated the slowing of neural activity.

V.6 CONCLUSIONS

We investigated power and phase information of PD-related changes in oscillatory neural activity during motor performance. In contralateral motor areas, activity was slower, i.e. alpha power had a lower frequency, in line with earlier reports about resting state activity. Slowing is therefore not characteristic for the default network but is modulated by motor performance. Interestingly, the degree of slowing depended on disease severity. The more advanced PD, the slower the neural activity, rendering the functional relevance of slowing likely. Moreover, neural slowing was dependent on different aspects of the UPDRS score during resting state and movement. We found slowing of neural activity in the alpha and beta frequency band, which indicates progressing motor impairment even though performance was indistinguishable between patients and controls. The UPDRS assesses motor performance as well as cognitive functioning. The fact that certain subscores are more predictive of neural slowing than others, and that this is different during resting state and performance suggests that different mechanisms might be responsible for the slowing during resting state and movement. It is thus unclear if the here-reported slowing can be

attributed solely to motor impairment. Future studies should explore whether slowing also correlates with cognitive impairment like PD-related dementia (Bosboom et al., 2006; Soikkeli et al., 1991), where slowing is more exacerbated.

V.7 ACKNOWLEDGMENTS

This work was supported by the Netherlands Organisation for Scientific Research (NWO grant # 452-04-344) and the Internationaal Parkinsonfonds (grant # IPF-2006-1). We thank Floor Buma for her assistance in collecting the MEG data.

V.8 SUPPLEMENTARY MATERIAL

PATIENT INFORMATION

Table V.3: Sex, age, dominant side of PD (DS), Hoehn-Yahr scale (HY), MMSE, and UPDRS total score as measured in the ON state, occurrence of freezing, and medication.

No.	Sex	Age	DS	HY	MMSE	$UPDRS_{total}$	Fr.	Medication
1	m	63	R	2.5	30	35	N	L-Dopa 375mg/ ropinirole 24 mg
2	m	82	L	3.0	29	71	N	L-Dopa 500 mg
3	f	54	L	2.0	30	22	N	L-Dopa 500 mg/pergolide 2 mg
4	f	62	L	2.0	30	38	N	selegiline 5 mg
5	m	76	R	3.0	27	25	Y	L-dopa 1500 mg/pramipexol 0.8 mg
6	m	63	R	3.0	29	26	Y	L-Dopa 625 mg
7	f	53	L	3.0	24	37	Y	L-Dopa 500 mg/pergolide 1 mg
8	m	74	R	3.0	30	62	Y	selegiline 10 mg/pramipexol 1,5 mg
9	m	76	L	3.0	30	62	N	L-Dopa 500mg
10	m	56	R	2.5	30	38	Y	L-Dopa 330 mg/ropinirole 18 mg mg
11	m	50	R	1.5	28	24	N	L-Dopa 375mg/pramipexol 2,1 mg
12	m	27	L	2.5	30	58	N	selegiline 5 mg
13	m	59	L	2.0	30	44	N	pramipexol 1,32 mg
14	m	59	L	2.5	28	47	Y	L-Dopa 375mg/ ropinirole 15 mg
15	f	76	L	3.0	30	40	Y	L-Dopa 187,5mg/ ropinirole 15 mg
16	m	63	R	2.5	29	71	Y	L-Dopa 1225 mg/pergolide 4mg
17	m	65	R	3.0	30	58	Y	L-Dopa 625 mg/pergolide 5 mg
18	m	63	L	3.0	30	56	Y	L-Dopa 1000 mg/pramipexol 2,8mg
19	m	74	L	2.5	29	50	Y	L-Dopa 625 mg
20	f	50	R	2.0	30	23	N	L-Dopa 625 mg/pergolide 1 mg

PERFORMANCE TEMPO

PD is often accompanied by a reduced movement tempo. With the external pacing we aimed for a (largely) identical movement tempo across participants, so as to ensure that changes in spectral composition of the accompanying cortical activity were not a mere by-product of altered performance. To investigate whether movement tempo stayed constant in the course of performance we determined movement frequency of the first and second half of each movement period. We found no significant difference in any of the conditions as shown in Figure V.8.

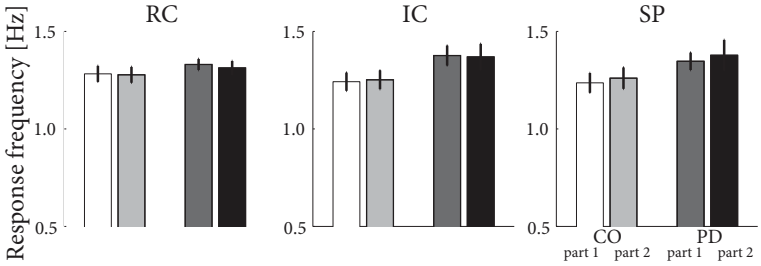

Figure V.8: Performance frequency during the three experimental conditions for the first and second halve of each movement period (averaged over movement periods for both the PD patients and the controls. There was no significant slowing for either group).

PD PATIENTS WITH PRONOUNCED TREMOR

To investigate any confounding influence of tremor in the PD patients, we analyzed the EMGs of the right flexors (*m. flexor carpi radialis*) and the corresponding event-related M1 activity. In fact, only two patients exhibited a tremor in the form of a pronounced peak in the EMGs' power spectra around 4-5 Hz. Despite this tremor, however, the power of the EMG and of the MEG at higher frequencies was similar to patients without a tremor, as can be seen in Figure V.9.

LOCATION OF PRIMARY MOTOR AREAS

For each subject we determined the task-relevant areas by comparing beta band power (13-30 Hz) during 3×20 s of movement with 3×20 s rest for the total of the three conditions. Peaks in the resulting differences were located and compared to the anatomical MR images. Locations of the peaks did not always fall precisely on the anatomical location of M1 but

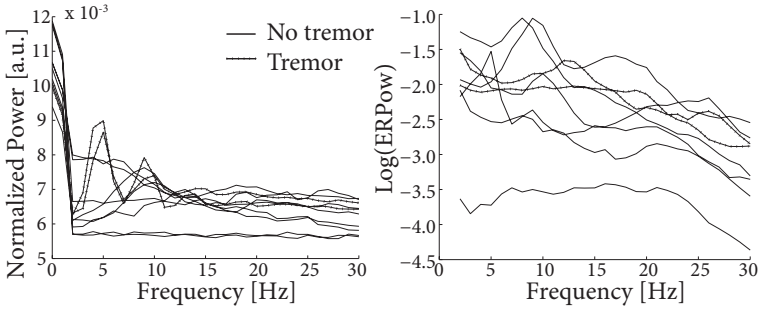

Figure V.9: Power spectrum of the EMG of the right flexors and the event-related power of the left M1 of the PD patients and controls. Two PD patients showed a tremor in the form of a peak around 4-5 Hz with a higher harmonic around 8-10 Hz. However, no such peaks can be seen in the event-related M1 activity.

were always sufficiently close to be incorporated in the subsequent analysis (unfortunately the MRIs contained large movement artifacts). These individual SAM beamformers were finally used to weight the corresponding MEG channels to reconstruct activity at M1 in all participants.

MEG POWER AND PHASE

MEG signals can be decomposed into amplitude and phase by using the Hilbert transform. ERpow was determined by first band-pass filtering MEG signals around frequencies $f = 7, 8, \ldots, 30$ Hz, and computing the Hilbert amplitude for time-series. Next, the result was averaged over the [-350, 350] ms epoch around each event. This yielded time-frequency (log) ERPow. These signals were averaged over time or frequency to yield time/frequency-series for ERpow.

ERpu was similarly obtained from the Hilbert phase of the band-pass filtered MEG time-series. These signals were then mean-centered (as base-line level values were not of interest here), Fisher transformed (Mardia, 1972), and finally normalized. This procedure ensured that baseline levels did not influence the analysis; the Fisher transform smoothes the variances so as to ensure applicability of the ANOVA.

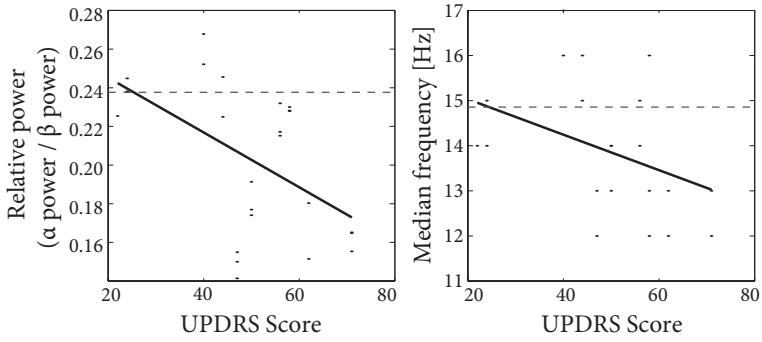

Figure V.10: Slowing of neural oscillations during resting-state. There was a significant influence of UPDRS score on *relative power* ($t_{23} = -3.01, p < 0.01$), but the effect on median frequency did not reach significance ($t_{23} = -2.04, p = 0.053$). The *relative power* and the *median frequency* of the PD patients differed significantly from those of the CO ($t_{51} = -4.06, p < 0.001$; $t_{51} = -2.80, p < 0.01$ respectively).

SLOWING OF NEURAL ACTIVITY DURING RESTING STATE

To compare these results to results based on resting state activity, we analyzed the resting state data for the PD patients in a similar fashion and compared them to the movement conditions. To this end we took three identical time intervals from the pre-movement rest period and performed the same analysis with surrogate events. These surrogate events were merely the actual pressure peaks shifted in time to coincide with the three rest periods. There was no difference between the PD and CO ERpow traces. However, there was a significant effect of UPDRS score on the relative power ($t_{23} = -3.01, p < 0.01$). The effect of UPDRS score on the median frequency was just above significance ($t_{23} = -2.04, p = 0.053$), see Figure V.10.

For the ERpu as a function of frequency we found a main effect of *group* ($F_{1,15} = 4.95, p < 0.05$). The primary principal component explained only 43% of the total variance. Similar to the ERpow values, there was a distinction between the alpha and beta bands. However, here the PD patients showed lower uniformity values in the alpha band and higher values in the beta band compared to the controls. The results are displayed in Figure V.11.

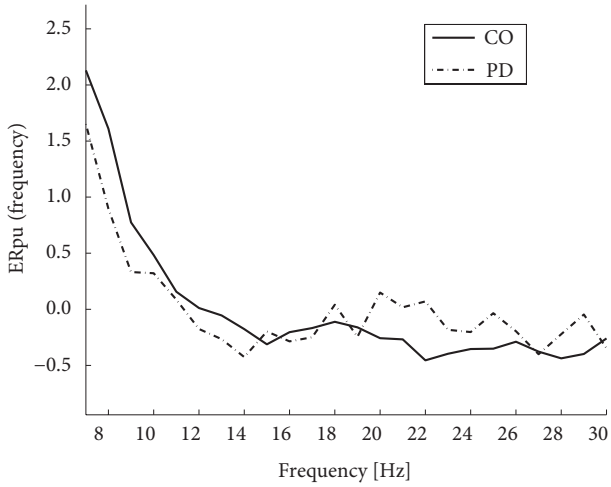

Figure V.11: Effect of group and condition on the ERpu frequency distribution. There was a significant effect of group ($F_{1,15} = 4.95, p < 0.05$). The primary PCA mode explained 43% of the total variance.

CHAPTER VI

EPILOGUE

VI.1 REVISITING THE RESEARCH QUESTIONS

The main body of this thesis consists of four studies aimed at examining how humans perform timed rhythmic movements using different types of perturbations. In this final chapter, I will discuss the implications of the main findings with regard to the research questions posed in Chapter I, which were framed as follows:

- Is the timer an object that can be manipulated independently of movement? Or, formulated conversely, can the timer be manipulated by movement?
- Is the interplay between the timers of two fingers characterized by a fixed phase relationship during the production of unimanual movements, or does it exhibit properties similar to those found during bimanual movements?
- Moreover, can this phase relationship be altered in a manner similar to how bimanual coordination patterns are changed?
- Are there changes in neural activity that persist beyond a bout of cued rhythmic movements into periods of rest?
- When investigating Parkinson's disease (PD), how does neural activity change during cued rhythmic movements, and how does this change depend on the severity of the disease?

THE CLOCK

Based on the results of Chapter II, the abstract notion of a clock appears appropriate because the results suggested that the clock can be manipulated and that changes in the clock transfer directly to changes in behavior. As the observed changes in behavior could be readily accounted for by changes in the clock, it is reasonable to conclude that the

notion of a clock or timer constitutes a valid concept in the study of motor timing, which can be usefully invoked in experimental studies of rhythmic timing.

Where does this leave timer models in general? First, a great body of literature supports the idea that such models describe several important characteristics of behavior rather well, and the study reported in Chapter II represents no exception in this regard. In particular, Chapter II provided additional evidence in favor of the additive structure of the Wing-Kristofferson model, thus strengthening the existing evidence for this timer model. Second, if the structure of the model corresponds well to behavior and the estimates of the autocorrelation function of the clock intervals correspond well to the actual autocorrelation function, the assumptions of the timer model indeed seem correct. Finally, the lack of a direct verification of the assumptions of timer models need not interfere with research based on such models.[1] When using timer models for describing or explaining behavior, one has already decided to focus only on timer intervals and to ignore many other relevant aspects of rhythmic movement; timer models provide a way of investigating interval timing but not other, continuous dynamic features of movement. The model one adopted corresponds to the nature of the question posed. In contrast, when we move to the issue of uniqueness of timers and phase relationships between the motor outputs corresponding to those timers, the clock no longer provides the level of detail necessary to resolve this issue. This is also the case when we consider neural activity in the brain. Instead, the concept of timing provides a way to answer timing related questions using a wide variety of techniques.

MIRROR MOVEMENTS

In Chapter III, mirror movements were employed as an expedient window into examining how multiple timers are coordinated during unimanual movements. The results revealed that mirror movements exhibit a wide distribution of phase relations with the active hand. As it turned out, this phase relation can be manipulated by priming the motor system to perform bimanual movements with a pre-defined phase relation. After performing a bimanual task with an in-phase relation, more in-phase mirror movements occurred. Conversely, after performing a bimanual task with an anti-phase relation, more anti-phase movements occurred, albeit that in this case the after-effect was weaker than for the in-phase coordination.

[1] Timer models typically assume that clock intervals and motor delays are statistically independent in time and statistically independent of each other, but this assumption has not yet been verified.

These results implied that the principles governing bimanual coordination are also operative during unimanual coordination, in line with the hypothesis that unimanual movements are instances of bimanual coordination with the motor output of one limb being suppressed. In addition, mirror movements offer a way of investigating the interaction between two timers. Ultimately, it would be interesting to know whether phase transitions also occur in mirror movements, although the incidence of mirror movements might be too low for this to be reliably established. It seems that there is no overarching clock that governs the timing of all individual limbs like a puppeteer pulling the strings in order to control the limbs of the puppet. Instead, it seems that the timing of two (or more) limbs in conjunction is the result of a complex interaction between different clocking mechanisms. This interaction extends even to unimanual movements in that it seems there is no single, localized clock that is responsible for the rhythmical movements of a single finger. That is, the brain does not seem to have a single neural structure that is responsible for the timing of each separate effector, but rather employs some form of distributed control in which multiple dynamic timers are responsible for and hence stand between effectors.

SWITCHING STATES IN PARKINSON'S DISEASE

Cueing therapy, i.e. the use of rhythmical stimulation to guide and improve the movements of patients, has profound beneficial effects on motor-related problems in PD. To investigate the neural underpinnings of those effects, Chapter IV examined movement-related after-effects in neural activity following different types of cueing. Switching from rhythmic movement production to rest is more demanding than previously thought. A period of 5 s after movement termination was identified in the beta band for both PD patients and healthy controls, where the identified change in neural activity indicated a larger recovery for regular cues compared to irregular cues. In the alpha frequency band, a late increase, 40 s after movement termination, lasting 30 s, was found for the controls, but was absent in the PD patients. This finding was interpreted as evidence for a long-lasting motor perseveration period, during which controls were able to relax allowing their brain to turn 'idle'.

As stated in Chapter IV, the prolonged motor recovery period has implications for MEG experiments using a block design as it implies that it takes in the order of 5 to 10 s for MEG activity to return to pre-movement resting state levels. When comparing movement vis-a-vis rest, it is essential to await transient behavior to have waned before starting to

analyze the recordings. Transients can corrupt the analysis in many ways. For example, most statistical estimators are only properly defined for stationary data. For the comparison of movement with rest the argument is even simpler: if the inactive period after movement involves more than simply rest (i.e. resting state before movement), this hysteresis effect renders the comparison inadequate, or at least nontrivial in block designs. The most striking result of Chapter IV involves the absence of activity that corresponds to settling into a relaxed state. This result was attributed to the motor perseveration phenomenon that was found in PD (Stoffers et al., 2001; Ebersbach et al., 1994). Collectively, the results of Chapter IV substantiate these findings and show that these effects can be measured by looking at MEG recordings.

The analyses reported in Chapter IV were rather tedious and did not yield support for the expected effects of different types of cueing. In previous studies, cueing effects have been demonstrated to greatly improve gait. In contrast, the rhythmic task used in Chapter IV (and V) might have been too subtle to display these effects, and the environment of the MEG shielded room too artificial compared to walking in daily-life settings. Above all, the subjects were investigated in the ON-state, thereby limiting reliable estimates of the potentially beneficial role of cueing in the OFF-state. The experiment relied on the fact that PD patients were able to perform the rhythmic squeezing task with similar accuracy as healthy controls. One might therefore argue that the experiment has limited value in investigating cueing in PD in general, i.e. one should include the OFF-state. Nevertheless, the experimental design was rather successful in terms of gaining insight into neural slowing in PD as will be discussed next.

NEURAL SLOWING IN PARKINSON'S DISEASE

Slowing of neural activity in PD has been shown in several studies using both EEG and MEG. However, these results are invariably based on resting state activity. In Chapter V, neural slowing was studied further by including periods of movement and by focusing on the relation between PD severity and neural slowing. Chapter V showed that slowing of neural activity is related to PD severity as measured by the UPDRS score. Slowing was present in PD patients during both rest and movement. The UPDRS score measures multiple facets of PD: motor problems, cognitive dysfunction, and performance of daily-life activities. The motor subscore proved to be the best correlate of slowing of neural activity during motor performance, whereas the ADL and mental functioning subscores were the

best correlates during the resting state. This suggests involvement of different pathways in the slowing of neural activity observed in PD.

The results reported in Chapter V open up new avenues for investigating slowing in PD by separating slowing of neural activity into components correlating with the UPDRS subscores. In the present thesis, only slowing during rest and movement was considered, where the division between motor and mental score seems logical. By performing experiments designed for specific parts of the UPDRS score, it may be possible to establish which functions are involved in the changes of neural activity in PD, and which functions remain unaltered. If this can be accomplished by using a single-subject level, therapy may be customized to target the worst affected properties of PD.

In PD, tasks involving timing such as walking (Morris et al., 1996; Kwakkel et al., 2007) and the perception and production of rhythm are impaired (Grahn and Brett, 2009; Harrington et al., 1998). As the motor cortex is densely connected to the basal ganglia, the slowing of neural activity in the cortex is only one of many aspects that are changed by PD. Indeed, changes in neural activity have been found in a number of structures in the basal ganglia (Brown, 2003, 2006; DeLong and Wichmann, 2007). The results from Chapter V suggest that changes in the neural activity accompanying those impairments increase as the disease progresses. In all likelihood, the changes found in other parts of the motor network will have similar relationships with disease severity.

The overarching aim of the present thesis was to gain more insight into motor timing. As mentioned above, various known properties of timing ranging from the more abstract notion of a clock, via the interplay of multiple timers during left/right coordination (or suppression), to new properties of timing in the course of pathology have been investigated with a certain measure of success. However, it turned out that not all of the questions posed in the *Introduction* could be adequately answered. In the next sections I will discuss some of the limitations of the research methods that were encountered in this thesis that caused these shortcomings. I will also sketch some possible ways to overcome those limitations, as well as future directions for experimentation and theory development.

VI.2 LIMITATIONS OF RESEARCH METHODS

THE USE OF ENCEPHALOGRAPHY TO VERIFY TIMER MODELS

To verify all the assumptions that need to be fulfilled when applying timer models, proper approximations of the clock intervals are indispensable. Each clock 'command' must be accurately identified to obtain a reliable estimate of the autocorrelation function of the clock. Errors in this identification process potentially result in a spurious negative lag-one autocorrelation, which renders any statement about the independence of clock intervals difficult if at all possible. This also implies that recording techniques with high temporal resolution are essential. These techniques should be non-invasive to allow for applications in 'daily' circumstances and to be acceptable from an ethical point of view. MEG (and its electrical counterpart EEG) is a serious candidate for such applications. Unfortunately, MEG/EEG recordings are very sensitive to all sorts of noise and, in particular, to movement artifacts. Noise does not only come from outside the brain, but indeed ongoing brain activity has spectral characteristics and correlative structures that largely resemble that of random or weakly colored/correlated noise. When focusing on event-related activity in certain functional areas like the motor cortices, all this noise typically causes a poor signal-to-noise ratio. Our own estimates in the context of simple tapping with the index finger revealed a signal-to-noise ratio as low as -10 dB. As said, the ongoing, or background, activity in the brain has a broad spectral content, which is also similar to that of the motor-related activity in the cortex rendering removal of noise by mere frequency filtering impossible. In consequence, following this event-related approach supplemented by frequency-selective filtering will probably not be sufficient to verify the assumptions of timer models.

THE USE OF MEG TO STUDY TIMING IN GENERAL

Many areas of the brain are implicated and thus active in the planning, execution, and control of timed rhythmic movements (Mayville et al., 2002). MEG merely measures the net result of an intricate network of neural populations in the cortex. Since other, deeper structures can only be assessed with great difficulty, it remains a challenge to draw conclusions about the more general mechanisms governing timing that may involve those deeper structures, such as the basal ganglia, the cerebellum and the brain stem. That is, the relationship between deeper structures and the cortex must be assessed by other means than MEG, such as anatomical connections and fMRI, but these may only

provide (spatial) constraints on timing mechanisms (e.g. regions of interest) as they lack the necessary temporal resolution. Obtaining a more complete picture involves piecing together information on different timescales and different physiological mechanisms. I believe that it will take decades if not centuries to overcome before all the relevant pieces of this picture will be found and put together. Only then will we be able to truly understand how motor timing is achieved by the human brain.

THE USE OF MEG EXPERIMENTS IN RELATION TO CUEING THERAPY

PD patients show similar levels of motor performance to controls in performing simple timing tasks. This is essential if one seeks to investigate changes in neural activity as a result of PD. As mentioned before, and discussed in Chapter IV, it is conceivable that at these similar levels of performance, differences in neural activity are too subtle to determine using MEG. Thus, the behavioral improvements found with cueing therapy are difficult to reproduce in any experimental setting where patients are requiring to perform equally accurate control subjects.

EXPERIMENTAL SETTINGS RESTRICT NATURAL BEHAVIOR

MEG has some technical limitations that have repercussions for experimental settings, and putting people in the MEG and asking them not to move, blink or speak significantly limits the subject in performing the required task. In addition, most subjects suffer from boredom and some even fall asleep. At present, MEG and EEG have the best temporal resolution of all non-invasive imaging techniques. Among high-temporal resolution imaging techniques, it also has the highest spatial resolution and, despite its shortcomings, remains invaluable in neuroscience.

VI.3 OVERCOMING THESE LIMITATIONS

ELECTROCORTICOGRAPHY (ECOG)

Popular techniques like EEG and MEG constitute no adequate means for verifying the assumptions of timer models due to their poor signal-to-noise ratio and the non-trivial problem of adequate filtering. An interesting alternative is ECoG, which is known to have a much better signal-to-noise ratio as it picks up electric potentials directly at the

cortex, and hence does not suffer from signal reduction caused by the impedance of skull and superficial tissue. The substantial price one has to pay is that one has to open the skull, which is of course highly invasive. ECoG is used to determine sources of epileptic activity in patients with such severe cases of epilepsy that the part of the brain that houses this source is removed (Kuruvilla and Flink, 2003). To this end, an array of electrodes is inserted under the skull allowing recordings from as many as 128 sites at high temporal resolution with virtually no cross-talk between recording sites. Presently, this technique is used to study the use and performance of brain-computer interfaces. With a temporal resolution of around 500 Hz, this technique is accurate enough for proper estimation of autocorrelations of timer intervals. The signal-to-noise ratio of ECoG seems to be good enough to estimate single motor events during rhythmic movements (Miller et al., 2007, 2009), thereby providing a very promising opportunity to verify the afore-discussed assumptions of timer models. One must keep in mind, however, that this technique is only applied to patients and that the conditions under which a patient can perform experiments are usually quite limited. In fact, it is possible that results obtained from a person suffering from severe epilepsy are not comparable to healthy individuals.

HIGH DENSITY EMG, INTRAMUSCULAR EMG, AND NEURAL RECORDINGS

Half of the Wing-Kristofferson model relates to motor delays. In principle, having access to the time onset of muscle activity and the movement event would provide an accurate measure of the peripheral part of the motor delay: all but the conduction time between the motor cortex and the motor neuron endplate would have to be incorporated. However, using conventional surface EMG, it is very difficult if not impossible to determine an unambiguous point in time corresponding to the onset of muscle activity with millisecond precision, even with the use of state-of-the-art techniques (Vannozzi et al., 2010). There are several other techniques which may be more fruitful in determining a reliable onset measure. High density EMG affords tracking of the activity of different motor units (Holobar et al., 2009), and even gives an indication of the number of motor units that are active (Williams et al., 2005). This technique is as easy to use as conventional EMG, but provides much more insight into muscle activity which can be used to monitor and track the progression of neurodegenerative diseases (van Dijk et al., 2010). A step further is the use of invasive measures to assess muscle activation. With intramuscular EMG, needles or wire electrodes are inserted into the muscle belly (Merletti and Farina, 2009). It is also

possible to record activity directly from neurons. Although this technique is substantially more unpleasant than high density EMG or intramuscular EMG, one has the ability to measure the output of the motor neurons to the muscle (Mano et al., 2006). By analyzing the autocovariance function of the motor delays, another aspect of timer models may be verified. Also, any non-linear or filtering properties of the muscle-tendon complex can be investigated to enhance our understanding of interval timing.

DEEP BRAIN RECORDING IN COMBINATION WITH MEG

Deep brain stimulation, where electrodes are inserted into deeper parts of the brain such as the subthalamic nucleus (Hamani and Lozano, 2004; Toda et al., 2004; Wichmann and Delong, 2006), has been shown to alleviate movement-related problems in PD (Benabid, 2003; DeLong and Wichmann, 2001; Lozano et al., 2002). The electrodes used for this stimulation can also be used to record activity (Valls-Solé et al., 2008). By combining recordings of the basal ganglia with recordings of the cortex, the results given in Chapters III and IV may be interpreted more easily. In addition, this affords simultaneous information of multiple structures which may clarify the involvement and interplay between those structures. Litvak et al. (2010) have recently succeeded in conducting simultaneous MEG and deep brain recordings. The experiments discussed in Chapters IV and V would greatly benefit from such combined recordings which allow more insight into attentional processes and timing properties. One possible drawback is that electrodes and the stimulation device can interfere with MEG recordings.

TMS TO INDUCE 'MOTOR COMMANDS'

Although not yet reported in the literature, I attempted to prescribe the clock output by means of transcranial magnetic stimulation (TMS). By imposing different autocorrelation structures for the clock by temporally precise TMS pulses, and having access to detailed EMG and force recordings, it might be possible to verify the Wing-Kristofferson model. Unfortunately, even though the pulses generated a minimal motor response, the resulting movement and EMG patterns were virtually identical. Normally, one finds a large variability in responses corresponding to the size principle (Henneman, 1957; Henneman et al., 1965); motor units are recruited from small to large with increasing motor drive. Single supra-threshold TMS pulses generate an all-or-nothing response in that all motor units seem to all fire at once which causes the responses to be identical. Motor delays, the time from

the TMS pulse to EMG onset was also virtually constant. Although the present approach was abandoned, it should not be discarded completely. If the size principle issue can be overcome, or if lower levels of stimulation can be used in conjunction with more sensitive recordings of muscle or nerve activity, TMS-induced timing might resemble interval timing more closely and can then be used to investigate timer models.

VI.4 FUTURE DIRECTIONS AND CONCEPTS

THE UNIT OF TIME

Timer models remain popular in the study of human movement (Vorberg and Wing, 1996; Repp and Steinman, 2010; Delignières et al., 2004; Wing et al., 2010). One aspect of these models has, however, not received much attention: the unit of time. In the seminal paper by Wing and Kristofferson (Wing and Kristofferson, 1973), the timer interval is made up out of a sum of base intervals. This construction implies the existence of a unit of time in the timing of rhythmic movement. It would be interesting to see if the neural networks involved in timing pose a structure that can produce units of time, similar to the way in which crystals in computers resonate at a certain frequency that defines the speed of the CPU. Investigations into a possible unit of time would involve experiments aimed at showing that humans generate time intervals (inter-response intervals or reaction times) that have a discrete distribution. Unfortunately, even if the neural output of the timer has this kind of distribution, the variability in muscle activation and muscle-tendon dynamics might mask this property. Recordings from sites higher up to the neural hierarchy would then be favored over behavioral measures.

THE RELATIONSHIP BETWEEN CONTINUOUS MEG ACTIVITY AND DISCRETE MOVEMENT

When we look at MEG recordings accompanying discrete rhythmic movements, we do not observe activity that resembles a discrete process. Rather, a waveform with a frequency corresponding to the movement frequency is seen. In Chapter V we showed event-related fields (ERFs) time-locked to the discrete squeezes of a bulb. There are several reasons that ERFs do not show a clear peak at the time of the movement command. First, MEG activity corresponds not to one focal site, but to the aggregated activity of many areas. Even if MEG records a, or 'the' clock, it certainly also records activity of other structures

that are involved when a movement is generated such as premotor and sensory areas. In consequence any method for locating functional areas potentially yields areas, with the size of a large marble, still does not guarantee that one has found the specific source of motor output or the clock (Baker, 2007). Second, to produce a discrete movement, more than one muscle is likely to be involved to ensure the movement is produced correctly. The time of activation of these muscles is by no means identical. On the other hand, if one could record only from the motor cortex during the performance of the simple movements, accompanying MEG activity might well be discrete. This indeed raises the question of the relationship of MEG activity to discrete events in more general terms. If we could extract discrete events from MEG, we could analyze clock intervals and enhance our understanding of timer models. In all likelihood, the combination of experimental data from invasive techniques such as ECoG with MEG recordings would provide the necessary insight.

THE CEREBELLUM

In the present thesis, the role of the cerebellum has hardly been discussed, even though it is a very important structure for the production of rhythmic movements (Houweling et al., 2008). Many studies, often involving lesions in the cerebellum, have shown that the cerebellum plays an essential role in the production of rhythms (Ivry, 1997; Ivry et al., 1988). The reason that the cerebellum has not been discussed that often is simple: the cerebellum is very hard to record. Typically, EEG and MEG sensors do not cover the lower back of the head. Moreover, the neck muscles, which produce considerable artifacts, stand between the cerebellum and the sensors. For a proper understanding of timing, activity in the cerebellum must be recorded. Unfortunately, this will have to be done by invasive techniques such as ECoG. The addition of recordings of the cerebellum with high temporal resolution in conjunction with deep-brain recordings from the basal ganglia, and MEG and/or ECoG recordings from the cortex will then cover the essential structures involved in the production of rhythmic movements.

BENEFITS OF INVASIVE VS. NON-INVASIVE METHODS

The preceding paragraphs suggest that the only way forward in studying the main topic of this thesis is to insert electrodes into the brain. Non-invasive methods have the advantage of being easy to use and readily accessible, but have major technical limitations. Invasive

methods, on the other hand, are very restricted in their general applicability due to ethical constraints, but have the potential to greatly advance our understanding of rhythmic movements and, for that matter, the brain itself. On top of ethics, we must also keep in mind that invasive methods always alter the way the brain works. That is, invasive techniques should not be used blindly just because they are available. The here-discussed methods are used in situations where those techniques provide essential aids for treating a disease. For example, deep-brain recordings help to adjust and confirm the efficacy of deep-brain stimulation in PD; the recordings and stimulation are conveniently provided by the same device. ECoG is used to determine the locus of epileptic tissue in patients who have no other option than to remove the derailed part of their brain. Having access to neural recordings accompanying the production of rhythmic movements using invasive techniques is a luxury for scientists studying patients. Such access is, at this time, not possible in healthy individuals and this should probably remain so.

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CHAPTER VII

ACKNOWLEDGMENTS

Cut, that's a wrap, and print. This section represents the end of a chapter in my life. And what a blast it has been. For the past four years (and a bit) many people have contributed to this thesis in different ways and I would like to use this space to give credit where credit is due.

Directors

Andreas, as my daily supervisor you have shared the ups and dows of my life as a PhD student and guided me through the process of becoming an independent researcher. More than that, you have shown me that mathematics alone won't solve real world questions and that sometimes you just have to get a feel for the data. As such, we have gone on many fishing expeditions and the cover of this thesis is a tribute to that. In turn, I have shown you the other side of experiments: actually being a participant and generating data (that will teach you to keep those protocols short). You have a found a great way of always being extremely busy but also always knowing when to take the time to help. As you have said many times (and only now do I believe you), all has indeed worked out well. I really enjoyed working together. Peter, you have taught me that writing down your research is not just a record of your activities and you showed me how to write a proper paper. I was always amazed when you returned a paper I handed in and saw that your version was exactly what I wanted to say.

Production technicians

The TOD. You have always been great in helping with the huge number of last-minute questions I came up with regarding sound equipment, rigging, video capture, and a couple of things actually related to my research.

On-site entertainment

All the PhDs and staff at FBW and the Analysis group at FEW, past and present. The gigs, sport tournaments, weekends, drinks, and good times that made my time at the VU University a lot of fun.

Partners in MEG

Sanne and Bernadette. You both performed MEG measurements like me. Together we formed a MEG anonymous meeting group where we could support each other through the trials and tribulations of MEG measurements and data processing. It worked well for me; I have been off MEG for six month now.

Office mayhem

My desk was located in A6.13. The years as a PhD student in the A6 corridor provided me with many hillarious days making research more fun and, at times, absolutely impossible. It is scary to think that some of you guys are now responsible parents.

High speed chases

The Friday Night Skate crew. Thank you for all the great tours of the city.

Gravity control

Sietske and Daphne, thanks for the great climbs indoors and outside.

Old school continuity

Dennis and Novandi, we go back a long way, even before the heavy metal, snowboarding, and crêpe ordering years. I really hope we can go boarding together again soon.

Overall support and opportunities

Mom and dad, you have always supported me and made it possible for me to follow my own path, thank you. John, thank you for showing me the Zen side of life. Stuart, Jonathan, thank you for being at my side during my defense. Near or far, you guys have always helped me out.

More love and good times than you can shake a stick at

Laura. I have never experienced my time as a PhD student as particularly stressful. Not because my PhD wasn't, but because there was always someone who made the rest of life so much easier and fun. You have always been there helping me out in ways not always clear to me. Thank you for the love, support, the great trips we have made and those that we will make in the future.

CHAPTER VIII

SUMMARY

Timing of movements is an integral aspect of human motor behavior. Rhythmic movements ranging from ordinary walking to playing a complicated piano piece rely heavily on correct timing. Even the simplest rhythmic movements are not without challenge; when the brain is affected by disease or injury, performing seemingly simple movements like walking can become quite a challenge. As all voluntary movements originate from neural signals produced by the brain, the investigation of timing naturally focuses on the brain. However, compared to the analysis of rhythmic movements, the analysis of brain signals associated with rhythmic movements is a rather difficult and hazardous affair. In moving only a single digit, many brain areas are involved in a complex interplay. In Chapter I, I discuss these issues in more detail and present a theoretical framework within which the techniques discussed in this thesis can be placed and interpreted in terms of the control and timing of movements.

As a starting point of this thesis, I decided to avoid the intricacies of the electrophysiology of the brain controlling timed movements, and depart from an abstract, mathematical model of the timing of movements based on theoretical concepts rather than highly detailed aspects of brain functioning. As humans are quite capable of producing rhythms at different tempos, many researchers have postulated that some kind of timer must reside somewhere in our brains. This timer is considered responsible for motor commands which eventually produce a response. Timer models have been employed to study the timing of movements that are synchronized to a metronome, that is, paced movements as well as self-paced movements. The simplest among those is the open-loop Wing-Kristofferson model, which consists of an internal timer or clock and motor delays that represent the time from the motor command to the time of the response. On the assumption that the timer intervals and the motor delays are independent, hierarchical processes that are similarly impacted by noise, the model predicts the temporal properties of rhythmic movements with remarkable accuracy.

The study reported in Chapter II discusses and extends the Wing-Kristofferson model. When tapping a desired frequency, subjects tend to drift away from this target frequency. This compromises the estimate of the correlation between inter-tap intervals (ITIs) as predicted by the Wing-Kristofferson model. Whereas previous studies on the timing of rhythmic tapping attempted to eliminate drift, the production of three constant frequencies (1.5, 2.0, and 2.5 Hz) was compared to the production of tapping sequences with linearly decreasing ITIs (corresponding to an increase in tapping frequency from 1.5 to 2.5 Hz). For all conditions, a synchronization-continuation paradigm was used. Tapping forces and electromyograms of the index-finger flexor and extensor were recorded and ITIs were derived yielding interval variability and model parameters, i.e. clock and motor variances. Electromyographic recordings served to study the influence of tapping frequency on the peripheral part of the tap event. The condition with an increasing frequency was more difficult to perform, as evidenced by an increase in deviation from the intended ITIs. In general, tapping frequency affected force level, inter-tap variability, model parameters, and muscle co-activation. Parameters for the condition with a decreasing ITI were comparable to those found in the constant frequency conditions. That is, although tapping with an intentional drift was different from constant tapping and more difficult to perform, the timing properties of both forms of tapping were strikingly similar and described quite well by the Wing-Kristofferson model.

Moving towards a more direct measurement of properties of the control of rhythmic movements, I investigated next the interaction between both hemispheres when unimanual movements are produced. It has been established that unimanual movements are not controlled solely by motor areas in the contralateral hemisphere, but rely on a bi-hemispheric interplay. When this interplay breaks down, mirror movements may be observed. Mirror movements are traditionally described as unintentional activity of the muscles homologous to those involved in a unimanual movement. By studying the dynamics of mirror movements, the timing of unimanual movements and the interplay between both hemispheres can be investigated.

The experiment presented in Chapter III focusses dynamical properties of mirror movements. Using a rhythmic isometric force production paradigm, after-effects of in-phase and anti-phase bimanual performance on the unintended recruitment of the homologous muscles of the opposite limb during subsequent performance of unimanual tasks were

investigated. Electromyograms obtained from the muscles of the opposite limb were analyzed in terms of their amplitude and the distribution of their phase relative to that of the intended movements. Preceding bimanual activity had distinct effects on the relative phase (mean and uniformity) of the structured electromyograms. These were particularly pronounced following performance of the in-phase pattern. These findings were discussed in terms of possible mechanisms of interhemispheric excitation and inhibition.

In many systems, great insight is gained by analyzing the system's behavior during perturbations. Obviously, perturbing the brain poses ethical problems. However, as the timing of movements is affected by diseases such as Parkinson's disease (PD), one may consider the Parkinsonian brain as a perturbed healthy brain. In PD patients, a major component in the generation of rhythmic movements, the basal ganglia, is disrupted. Besides the familiar tremor, motor problems such as shuffled or unstable gait and initiating movements increase progressively. As the basal ganglia and the motor areas are directly and indirectly coupled, the changes in the basal ganglia extend to the motor areas that can be investigated using MEG. Unfortunately, PD is not a curable disease. Thus much effort has been put into developing methods to reduce the symptoms of PD. Great advances have been made in reducing some of the characteristic motor problems associated with PD. Recently, for instance, a therapy has been successfully implemented that uses external rhythmic cues to help improve the motor performance and timing of PD patients. As part of a large study investigating the effects of cueing therapy, a paradigm involving cued and self-paced movement was performed at the MEG facility of VU Medical Center. These data were analyzed in Chapters IV and V.

Parkinson's disease is characterized by motor and cognitive problems that are accompanied by slowing of neural activity, even in early stage PD. Slowing is typically studied during resting state. Chapter V extends the study of this phenomenon from resting state to movement by comparing the relationship between neural slowing and disease severity during rest and motor performance. Primary motor activity was assessed by means of magnetoencephalography (MEG) during rest and rhythmic movements. Motor output and event-related cortical power in the alpha and beta frequency bands were determined. UPDRS total and subscores were used to pinpoint the predictors of neural slowing (change of power toward slower frequencies) during both resting state and the production of rhythmic movements. By design, motor performance was similar for patients and controls. PD

patients showed slowing of neural activity which increased with disease severity. Slowing during rest was best predicted by the cognitive subscore, whereas slowing during movement was best predicted by the motor subscore. These results suggest that slowing is functionally modulated and that different mechanisms are responsible for neural slowing during rest versus movement. Neural slowing must be viewed in a broader context than previously thought because it is not solely related to impaired motor performance but also impaired cognition.

PD not only affects the ability to move in a controlled manner, but also the ability to change behavior. A striking example is 'freezing' where a patient wants to start walking only to find him- or herself unable to move. Once a patient begins to walk, termination of this movement can also be affected. In light of the problems of switching from one type of behavior to another, after-effects of rhythmic activity can give insight into the way rhythmic movements are processed in the Parkinsonian brain and how the beneficial effects brought about by cueing therapy facilitate switches.

Chapter IV reports a study of the effects of Parkinson's disease on the production of rhythmic movements. External rhythmic cueing is known for its capacity to improve motor performance in PD patients. The neural correlates of these beneficial effects, however, are largely unknown. We examined the cortical activity accompanying rhythmic force production under two types of tactile cueing, regular and irregular, using MEG, and expected the cortical activity in the alpha and/or beta frequency range to respond differently to the different types of cueing, in the absence of differences in motor performance. Twenty early-stage Parkinson patients and fifteen age-matched healthy controls performed series of cued and self-paced rhythmic movements separated by rest. Each series was performed in the presence of regular or irregular cues. Using linear beamformers, MEG recordings revealed dominant motor-related activity in bilateral M1s. We found increased beta activity during the post-performance resting state compared to the pre-performance resting state. This beta rebound lasted 5 to 10 s in PD patients and controls alike and its strength depended on the presence of cueing and its type. In addition, we found a late and more sustained effect in the alpha band where the amplitude increased 40 s after movement termination. Although the quality of motor performance was similar for patients and controls, the after-effect in the alpha band was absent in the PD patients. It was thus concluded that motor perseverance is responsible for the absence of the increase in alpha power in PD patients.

Chapter VI summarizes the findings of the thesis and discusses them in light of current theories on the timing of movements. The validity and falsification of timer models is discussed in terms of experimental designs involving transcranial magnetic stimulation and the use of subdural electrodes in the brain. In addition, the results of the MEG studies reported in this thesis are compared to results using more invasive techniques and possibilities for future research are discussed.

Coda: this thesis first discussed the Wing-Kristofferson model for the timing of repetitive movements. The behavioral and encephalographic results discussed in Chapters II through V suggested that the timer in this model is rather oversimplified. Motor timing emerges from the interplay between different brain areas and capitalizes on the bilateral organization and interconnectivity of both hemispheres. The timer is thus not a fixed entity located somewhere in the brain, but exists by grace of a large dynamic network involving a large part of the brain. Therefore, gaining access to the timer and its properties is limited, constraining us to view this multifaceted object only one side at a time. Aggregation of the findings of this thesis and the aforementioned discussion will set the stage for future directions of research.

CHAPTER IX

NEDERLANDSE SAMENVATTING

Adequate timing van bewegingen is een essentieel onderdeel van onze motoriek. Ritmische bewegingen variërend van alledaagse activiteiten als lopen tot het spelen van een pianoconcert zijn afhankelijk van een goede timing. Bij ziekte of letsel kan de timing van de meest eenvoudige bewegingen ernstig zijn aangedaan, met alle gevolgen vandien voor de kwaliteit van de motoriek. Het onderzoek in dit proefschrift is gericht op het verwerven van meer inzicht in de timing van bewegingen, met name in relatie tot de onderliggende hersenactiviteit. Hoofdstuk I behelst een inleiding op deze thematiek en gaat in op bij het onderzoek gebruikte concepten en technieken.

Vertrekpunt voor het onderzoek is een wiskundig model voor de timing van ritmische bewegingen, dat een timingsmechanisme (of klok) in het brein veronderstelt. Modellen die gebaseerd zijn op een dergelijke klok, ook wel timekeeper- modellen genoemd, worden gebruikt om ritmische bewegingen, die al dan niet door een metronoom worden voorgeschreven, te bestuderen. Het meest eenvoudige timekeeper-model is dat van Wing en Kristofferson. Dit model bestaat uit slechts een klok en een vertraging die samenhangt met neurale looptijden. Het model gaat ervan uit dat het door de klok gegenereerde tempo en de eerder genoemde vertragingen onafhankelijk van elkaar zijn en elk gekenmerkt worden door een eigen variantie. Ondanks zijn eenvoud geeft dit model een adequate beschrijving van veel eigenschappen van het produceren van een vast tijdsinterval zonder metronoom, nadat dit tijdsinterval eerst werd gespecificeerd door een metronoom (het zogenoemde synchronisatie-continuatie-paradigma).

Hoofdstuk II beschrijft een experiment waarin het tikken met drie vaste tempi (1.5, 2.0, en 2.5 Hz) werd vergeleken met het tikken van een reeks van lineair afnemende inter-tik-intervallen. Voor alle tempi werd een synchronisatie-continuatie-paradigma gebruikt, waarbij mensen eerst met een metronoom het, al dan niet veranderende, tempo volgden en vervolgens het tempo verder zonder metronoom uitvoerden. Het veranderende tempo bleek

moeilijker uit te voeren dan de constante tempi. Ook werd gevonden dat het bewegingstempo invloed had op de uitgevoerde kracht, de variatie van de inter-tik-intervallen en de co-contractie van de vingerspieren. Deze resultaten werden gemodelleerd in termen van een aangepaste versie van het Wing-Kristofferson-model, waarbij de optredende drift apart werd gemodelleerd. De modelparameters werden geschat op basis van de variabiliteit en de inter-tik-intervallen en de daarbij geproduceerde kracht- en spieractiviteit. Het bleek dat deze parameters tijdens de constante tempi en het veranderende tempo sterk met elkaar overeenkwamen. Daaruit werd geconcludeerd dat het Wing-Kristofferson-model ook van toepassing is op de laatstgenoemde situatie.

Om meer inzicht te krijgen in de neurale aansturing van ritmische bewegingen werd vervolgens in Hoofdstuk III de interactie tussen beide hersenhelften onderzocht tijdens het uitvoeren van unimanuele bewegingen. Eerder onderzoek heeft aangetoond dat bewegingen met één ledemaat niet uitsluitend door de contralaterale hersenhelft worden aangestuurd, maar dat er sprake is van een bilaterale interactie. Wanneer deze interactie wordt verstoord, kunnen spiegelbewegingen optreden. Spiegelbewegingen zijn het gevolg van onbedoelde activiteit van homologe spieren die corresponderen met de spieren die bij de unimanuele beweging betrokken zijn. In het in Hoofdstuk III gerapporteerde experiment werden de dynamische eigenschappen van spiegelbewegingen nader onderzocht als functie van daaraan voorafgaande bimanuele ritmische bewegingen, die in in-fase of in tegen-fase werden uitgevoerd. De verdeling van de relatieve fase van de spiegelbewegingen ten opzichte van de unimanuele bewegingen bleek beïnvloed te worden door het eerder uitgevoerde bimanuele coördinatiepatroon (in- of tegen-fase), vooral als dit een in-fase-patroon betrof. Deze bevindingen werden geïnterpreteerd in termen van mogelijke patronen van excitatie en inhibitie tussen beide hemisferen.

Hoofdstuk IV beschrijft een studie naar de effecten van de ziekte van Parkinson op de productie van ritmische bewegingen en de daarmee corresponderende hersenactiviteit. Hierbij werden ritmische stimuli aangeboden om de beweging te begeleiden. Dit heeft een gunstig effect op de motoriek van patiënten met de ziekte van Parkinson. Echter, de neurale basis voor dit effect is nog vrijwel geheel onbekend. De studie richtte zich op de neurale activiteit in de motorische hersenschors tijdens al dan niet door externe stimuli voorgeschreven ritmische bewegingen. Met behulp van magnetoenchephalografie (MEG) werden neurale bronnen in de hersenen gelokaliseerd die betrokken zijn bij de aansturing van de bewe-

gingen. De activiteit in de desbetreffende gebieden vertoonde opvallende na-effecten van de bewegingen in zowel de alpha- als beta-band. De effecten in de betaband wezen op een herstelperiode waarin de hersenactiviteit pas na enige seconden teruggekeerd was op het rustniveau. Deze effecten werden bij zowel gezonde proefpersonen als bij patiënten met de ziekte van Parkinson gevonden. De effecten in de alphaband verschilden tussen beide groepen in de zin dat de na-effecten langer aanhielden bij de patiënten. Dit resultaat werd geduid als een neuraal aspect van het perseveratieverschijnsel waarbij patiënten de neiging hebben te volharden in het actueel uitgevoerde gedrag.

Naast motorische problemen hebben patiënten met de ziekte van Parkinson ook cognitieve problemen. Beide typen problemen gaan gepaard met een vertraging in de activiteit in de motorische hersenschors in de zin dat de lagere frequenties een hogere spectrale inhoud krijgen. In Hoofdstuk V werd het verband tussen deze vertraging en de ernst van de ziekte nader onderzocht. Het eerder genoemde effect werd niet alleen in rust gevonden, maar ook bij het produceren van ritmische bewegingen. In beide gevallen bleek de vertraging sterker naarmate de ziekte verder was gevorderd. De ernst van de ziekte werd bepaald met behulp van de Unified Parkinson's Disease Rating Scale (UPDRS), die een motorische en een cognitieve subscore oplevert. Tijdens rust correleerde de neurale vertraging het sterkst met de cognitieve subscore, terwijl tijdens de uitvoering van bewegingen de correlatie met de motorische subscore het sterkst was. Geconcludeerd werd dat neurale vertraging specifiek is voor situaties waarbij de motorische of juist de cognitieve beperkingen een belemmering van de taak vormen.

Hoofdstuk VI vat de bevindingen van de bovengenoemde hoofdstukken samen en zet deze af tegen verschillende theorieën over timing van bewegingen die in Hoofdstuk I zijn besproken. De validiteit van timekeeper-modellen wordt bekrachtigd door de resultaten uit Hoofdstuk II. Voor het verder onderzoeken van de falsifieerbaarheid van de timekeeper modellen worden experimenten voorgesteld die gebruik maken van technieken als transcraniale magnetische stimulatie en subdurale elektroden. De interactie tussen timers bij unimanuele bewegingen blijkt eigenschappen van bimanuele bewegingen te vertonen als gekeken wordt naar de manier waarop de spieractiviteit gecoördineerd is. Ook worden de mogelijkheden van de hierbovengenoemde (invasieve) technieken vergeleken met die van MEG en vervolgonderzoeken voorgesteld. Het probleem dat patiënten met de ziekte van Parkinson hebben met het wisselen tussen gedragingen, weerspiegelt zich in

de daarmee geassocieerde hersenactiviteit en heeft zelfs na ruim een halve minuut na het stoppen van bewegingen nog effect op deze activiteit. De vertraging in neurale activiteit die in deze patiënten werd gevonden blijkt niet alleen afhankelijk te zijn van de ernst van de aandoening, maar ook van de vereiste vaardigheden (motorisch of cognitief).