Supraspinal control of walking:
lessons from motor imagery

Maaike Bakker

The research presented in this thesis was carried out at the Donders Institute - Centre for Cognitive Neuroimaging of the Radboud University Nijmegen, and at the Departments of Neurology (Parkinson Centre Nijmegen) and Rehabilitation of the Radboud University Nijmegen Medical Centre. The PhD student was employed at the Department of Neurology of the Radboud University Nijmegen Medical Centre, the Netherlands.

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Supraspinal control of walking: lessons from motor imagery

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Promotor:
Prof. dr. B.R. Bloem

Copromotores:
Dr. I. Toni
Dr. S. Overeem

Manuscriptcommissie:
Prof. dr. ir. D.F. Stegeman
Prof. dr. J.E.J. Duysens (KU Leuven)
Dr. W.P. Medendorp

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C1

General introduction and outline of thesis

General introduction and outline of thesis

Walking seems such a simple movement. We do it every day, usually without paying conscious attention: walking in crowded places, running to catch a train, climbing stairs, and so on. We can easily adapt our walking movements to new circumstances, again without much conscious effort. However, human walking is actually a surprisingly complex motor act, requiring a fine coordination of the head, trunk and all four limbs, with complex synergistic muscle activation patterns that allow for motion across many joints. Essentially, walking is the result of an intricate interplay between three important skills: a) locomotion: the ability to initiate and maintain rhythmic stepping; b) equilibrium: the ability to assume an upright posture and maintain balance; and c) adaptation: the ability to adapt movements to motivational and environmental demands. Performing these skills adequately requires appropriate biomechanics as well as flexible neural control. Any type of dysfunction in any of these systems can disturb gait. This is precisely why gait is so vulnerable to pathology and why so many different diseases lead to gait disorders (Alexander and Goldberg, 2005; Snijders *et al.*, 2007). One example that will be addressed in more detail in this thesis is Parkinson's disease (PD) (Box 1.1). Gait disturbances in PD can have a major impact on quality of life. They may result in injury due to falls (Pickering *et al.*, 2007). Furthermore, severe gait problems render patients less mobile, leading to a loss of independence and reduced fitness. Treatment is generally difficult (for a review see Boonstra *et al.*, 2008), although off-period symptoms can improve with higher doses of antiparkinson medication. Some physiotherapeutic interventions are also effective, including in particular the technique of cueing (Keus *et al.*, 2007; Nieuwboer *et al.*, 2007). Yet even with current optimal medical management, many patients remain considerably handicapped because of persistent gait problems. Unfortunately, development of new therapies is hampered by the current lack of insight into the neural mechanisms and circuitries underlying gait control in health and disease.

Neural control of gait

Most knowledge about the neural control of gait in mammals comes from experiments in cats and rodents. This work has shown that the neural control of walking in quadrupeds is based on the integrative function of a number of systems at different levels of the nervous system. First, there is a network in the spinal cord which has the ability to generate the basic locomotor rhythm (spinal central pattern generator; CPG) (Duysens and Van de Crommert, 1998; Grillner and Wallen, 1985). In order to adapt the basic locomotor pattern to motivational and environmental demands, the CPG depends on inputs from peripheral afferents and supraspinal structures (Drew *et al.*, 2004; Pearson, 1995). For example, the mesencephalic locomotor region (MLR), contains neurons that lead to the production of locomotion when electrically or chemically stimulated in a decerebrate cat (Garcia-Rill and Skinner, 1987). This region is therefore thought to be involved in the initiation and regulation of the stepping pattern. The motor cortex seems essential for adapting the locomotor movements to the environmental context in which they are executed (Armstrong, 1988). For example, cats with disruption of the corticospinal tract have minimal problems with normal overground walking, whereas they have great difficulties when precise foot positioning is required, such as while walking along a narrow beam or a horizontal ladder (Liddell and Phillips, 1944).

Recent studies have shown that in humans the influence of supraspinal structures on gait control is more dominant than in other animals. For example, spontaneous rhythmic activity of the legs following complete spinal cord injury is rare in humans (Bussel *et al.*, 1996; Calancie *et al.*, 1994), although rhythmic stepping movements can be elicited in such patients when they are placed on a moving treadmill with their weight supported and they are provided with appropriate afferent input (Dietz, 2008). Furthermore, supraspinal lesions typically have a much more debilitating effect on

walking in humans than in animals. This was first seen in patients with sensory or – in particular – motor strokes, indicating that supraspinal motor and sensory systems are involved in regulating human gait. Subsequent work showed involvement of virtually all parts of the motor system, and focal lesions can produce a specific matching gait abnormality: ataxic gait in patients with cerebellar disease, spastic gait in patients with pyramidal tract lesions, or hypokinetic-rigid gait in patients with basal ganglia disease (Snijders *et al.*, 2007; Nutt *et al.*, 1993).

Box 1.1 Gait disturbances in Parkinson's disease

Gait disturbances are among the primary symptoms of Parkinson's disease (PD) (Boonstra et al., 2008). In early stages of the disease, mild gait or postural abnormalities may be present, including an asymmetrically reduced or absent arm swing, a gently stooped posture, and difficul-ties turning around. As the disease progresses, gait becomes slower and the typical parkinsonian gait emerges with shuffling and short steps, a bilaterally reduced armswing and slow turns which are executed "en bloc". Besides these continuous gait problems, some patients may experience brief and sudden moments where the feet subjectively become glued to the floor ("freezing of gait"). The prevalence of this "paroxysmal" gait disorder increases with disease duration and progression of disease severity (Giladi et al., 2001). It is also more common after prolonged dopaminergic treatment, but can occur in drug-naïve patients. Freezing episodes are typically brief usually lasting only several seconds, but may persist for minutes in more advanced stages of the disease. It most commonly appears while patients are making turns, but may also occur spontaneously during straight walking, while crossing narrow spaces, when patients try to initiate gait ("hesitation") or when patients reach a target (Schaafsma et al., 2003). Shuffling with small steps or trembling of the legs is much more common than complete akinesia (Bloem et al., 2004).

Interestingly, poorly mobile PD patients with severe gait problems can sometimes respond quickly to environmental events and move unexpectedly well. This phenomenon is termed "kinesia paradoxica" and is typically triggered by emotional or threatening circumstances. In contrast, performing a secondary task during walking significantly worsens gait. For example, gait problems increase when patients have to walk while carrying a tray with glasses, or while reciting arithmetic sequences (Bloem et al., 2006; Bond and Morris, 2000; Morris et al., 1996).

Figure 1.1 *Illustration of Parkinson's disease by Sir William Richard Gowers from A Manual of Diseases of the Nervous System in 1886.*

More recently, new work has drawn attention to the important influence on gait played by neuropsychological processes such as attention, and by cognitive functions such as frontal executive functions (Yogev-Seligmann *et al.*, 2008). Gait was originally considered to be a largely automatic task, regulated mainly by subcortical control mechanisms and requiring little if any conscious attention. In contrast, gait is now increasingly seen as a complex 'higher-order' form of motor behaviour, with prominent and varied influences of mental processes. The importance of cognition in gait control is underscored by the gait problems observed in patients with cognitive decline (Shaw, 2002; van Iersel *et al.*, 2004), and by the profound effect of dual tasking on gait performance (Lundin-Olsson *et al.*, 1997; Woollacott and Shumway-Cook, 2002).

The above described work demonstrates the importance of supraspinal structures in the control of human gait. Insight in the roles of each of these different structures in this process is limited though. Especially, the role of cortical structures remains largely unclear. This is mainly due to technical difficulties: until recently there was no animal model of bipedal gait (Mori *et al.*, 2004), and examining the supraspinal control of human gait is not straightforward.

Examining the supraspinal control of human gait

The development of neuroimaging techniques has made it possible to examine the supraspinal control of human movements, in ways that were hitherto impossible. Prior approaches were restricted to indirect comparisons, for example between clinical observations made during life and post-mortem neuropathological findings. However, while theoretically attractive, neuroimaging of gait is not straightforward. For example, *structural* neuroimaging of patients with gait disorders has provided limited insights, given that cerebral lesions causing higher-level gait disorders are typically multifocal, or even diffuse as in leukoaraiosis (Masdeu, 2001). In addition, *functional* neuroimaging poses further specific practical problems, since techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI; Box 1.2) or electroencephalography (EEG) require subjects not to move during sampling of task-related cerebral activity. Several different approaches have been developed to overcome these problems. First, a few neuroimaging techniques are available that can assess cerebral activity during actual gait. These involve nuclear neuroimaging techniques (Fukuyama *et al.*, 1997; Hanakawa *et al.*, 1999b; Ouchi *et al.*, 2001) and near-infrared spectroscopy (NIRS) (Harada *et al.*, 2008; Miyai *et al.*, 2001; Suzuki *et al.*, 2004; Suzuki *et al.*, 2008). Other approaches that have been used is to record cerebral activity during motor planning of walking prior to walking initiation (do Nascimento *et al.*, 2005; Vidailhet *et al.*, 1993; Yazawa *et al.*, 1997), and to use tasks that share some cerebral processes with gait, without the need to engage in actual gait (like motor imagery of gait, or repetitive foot movements (Christensen *et al.*, 2000; de Jong *et al.*, 2002; Miyai *et al.*, 2001; Sahyoun *et al.*, 2004)). *Chapter 2* will discuss the contribution of these different approaches to the understanding of the cerebral control of gait in humans, both in healthy subjects and in patients with Parkinson's disease. Furthermore, a critical discussion of advantages and disadvantages of each these approaches will be provided. In *Chapters* 3-6, one of these approaches, namely motor imagery of gait, will be used to further examine the supraspinal control of human gait.

Motor imagery of gait

Motor imagery involves the mental simulation of an action without its actual execution (Jeannerod, 2006; Munzert *et al.*, 2009; de Lange *et al.*, 2008). It has been argued that the internal simulation of an action, as evoked during motor imagery, constitutes the core element of a motor plan (Jeannerod, 1994). The approach is based on the reported behavioural, physiological and neural overlap between imagining a movement, preparing a movement and executing a movement (Jeannerod, 1994). For example, it was found that the time it takes to imagine a certain action is closely cor-

related with the actual execution time of the action (Parsons, 1994; Sirigu *et al.*, 1996; Stevens, 2005). Furthermore, several neuroimaging studies have found that brain areas that are active during simulated actions, are also engaged in planning and preparation of movements (Deiber *et al.*, 1996; Hanakawa *et al.*, 2008; Rushworth *et al.*, 2003; Toni *et al.*, 2001). This behavioural and neural overlap suggests that motor imagery, motor planning and motor execution (at least partly) rely on common processes.

Box 1.2 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a method that uses MRI to investigate which areas of the brain are active during performance of a specific task (Huettel et al., 2004; Fig 1.2). It was developed in the early 1990s (Kwong et al., 1992; Ogawa et al., 1990), and since then has grown to become the dominant technique in cognitive neuroimaging.

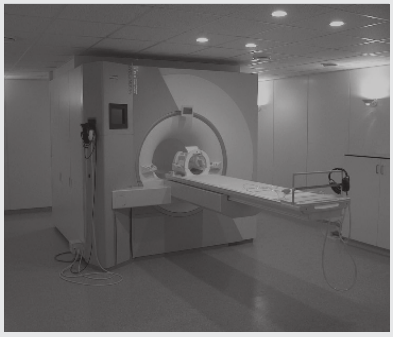

Figure 1.2 *Photograph of the MRI scanner used in our experiments. The main magnetic field of this scanner is 3 Tesla.*

An advantage of fMRI is that it allows for noninvasive recording of brain signals, without the risk of for example radiation that is used by some other neuroimaging techniques such as CT scans. In addition, it allows for recording with a high spatial resolution of 3-6 mm. A dis-advantage is that the temporal resolution is relatively low compared to techniques such as electroencephalography (EEG). This is related to the fact that fMRI does not measure neural activity directly. Rather it measures the changes in blood flow and blood oxygenation in the brain related to neural activity in the brain.

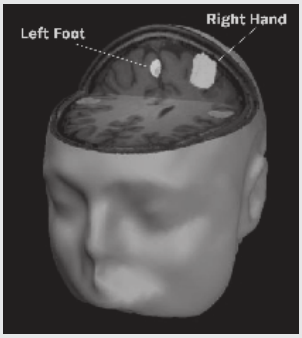

Figure 1.3 *An image of the brain with areas of statistically significant activity during task performance compared to rest (left foot movements-rest, or right hand movements-rest) indicated in colour. (Erik van den Bergh, Siemens Medical solutions)*

fMRI cannot detect absolute activity of brain regions. It can only detect differences in brain activity between several conditions. During the fMRI experiment, the subject is therefore asked to alternatively perform several tasks. Each of these conditions is repeated several times and can be separated by rest periods. It is im-portant that the experimental and control conditions are as similar as possible. If the conditions differ in more than one way, there could be multiple explanations for the differences in cerebral activity.

Motor imagery is particularly useful to examine the supraspinal control of gait for several reasons. First, there are practical advantages since motor imagery does not involve any actual movements, and subjects can be studied while they remain in a recumbent position. As such, this approach allows for the use of imaging techniques such as fMRI and PET. This is important, since these techniques provide relatively high spatial resolution and whole-brain coverage. Furthermore, there are also conceptual advantages in using motor imagery. Motor imagery would allow one to specifically examine the problems with planning of gait, while avoiding sensory and motor confounds related to motor execution.

Box 1.3 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive method to activate neurons in the brain. It uses an electromagnetic coil that is held over the subject's head. When current passes through the coil, it generates a magnetic field that can penetrate the subjects' scalp and skull. By rapidly changing the magnetic field, weak electric currents can be induced in the nearby brain tissue (electromagnetic induction). This allows for triggering brain activity with minimal discomfort.

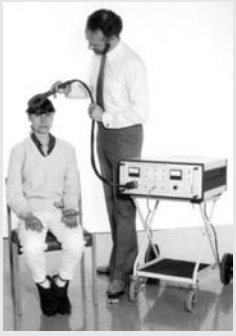

Figure 1.4 *Anthony T. Barker with the stimulator that was used to deliver TMS for the first time (Barker et al., 1985).*

When TMS is applied over the primary motor cortex, it produces a response that can be seen directly, in the form of muscle twitches. This response results from the activation of corticospinal neurons in the motor cortex that project directly to the spinal cord and that are connected in the spinal cord with alpha motor neurons which activate the muscles. The motor response induced by TMS is called the motor-evoked potential (MEP) and can be recorded with electromyography. The amplitude of the MEP reveals the net excitability of the corticospinal system (Rothwell et al., 1991). TMS studies have contributed considerably to our understanding of the role of the motor cortex and corticospinal tract in motor control (Petersen et al., 2003; Siebner and Rothwell, 2003).

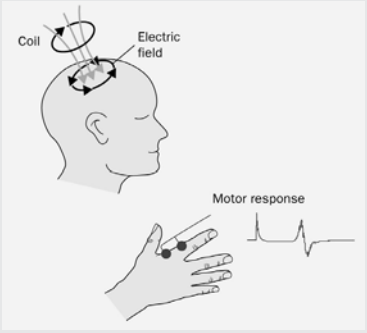

Figure 1.5 *The basic principle of TMS (adapted from Kobayashi and Pascual-Leone, 2003). The current flowing briefly in the coil generates a changing magnetic field that induces an electric current in the tissue, in the opposite direction. When TMS is applied over the primary motor cortex, it produces a motor response that can be recorded with electromyography.*

Several studies have already used motor imagery to examine the cerebral structures involved in the planning of gait (Jahn *et al.*, 2004; Wagner *et al.*, 2008; Deutschlander *et al.*, 2008; Wang *et al.*, 2008; Iseki *et al.*, 2008; Malouin *et al.*, 2003; Jahn *et al.*, 2008; Miyai *et al.*, 2001; Sacco *et al.*, 2006). For example, Malouin et al (2003) used $H_2{}^{15}O$-PET to compare cerebral activity evoked during motor imagery of standing, initiating gait, walking, and walking with obstacles. However, this and other studies could not provide objective behavioural evidence that the subjects were specifically engaged in motor imagery of gait during the experiment. This is important given the importance of sampling cerebral activity during tasks that patients can perform effectively (Price and Friston, 1999). Therefore, one of the aims of this thesis is to develop a new protocol that allows for monitoring task performance during motor imagery of gait in a neuroimaging setting (*Chapter* 3).

Before using this new protocol to examine gait problems in patient populations, it is important to make sure that the motor imagery task evokes specific responses within the motor system. Therefore, fMRI will be used to examine the cerebral structures involved in motor imagery of gait (*Chapter* 4). Given that the protocol involved a manipulation of path width (subjects had to imagine walking along a narrow (9cm) and a broad path (27 cm)), it allowed for examining the cerebral structures involved in motor imagery of both normal and precision gait (gait requiring precise foot placement and increased postural control) (*Chapter* 4). In addition, transcranial magnetic stimulation (TMS; Box 1.3) will be used to examine whether motor imagery of gait is accompanied by an increase in corticospinal excitability (*Chapter* 5). Motor imagery of both complex and simple hand movements induces a muscle-specific and temporally modulated increase in corticospinal excitability (Fadiga *et al.*, 1999; Fourkas *et al.*, 2006a; Kuhtz-Buschbeck *et al.*, 2003; Rossini *et al.*, 1999; Stinear and Byblow, 2004). However, evidence for changes in corticospinal excitability during motor imagery of leg movements is limited (Hiraoka, 2002; Tremblay *et al.*, 2001), and no study has examined changes in corticospinal excitability during motor imagery of gait.

Motor imagery of gait in Parkinson's disease

Motor imagery might be particularly useful to study the cerebral control of gait in PD, given that there are indications that motor problems in PD are partly caused by problems with motor planning. For example, PD patients mainly have problems with performance of internally rather than externally cued movements (Georgiou *et al.*, 1993; Georgiou *et al.*, 1994; Jones *et al.*, 1992), and with performance of complex and sequential movements rather than simple repetitive movements (Benecke *et al.*, 1986). Such complex sequential and non-externally cued movements require a greater degree of internal planning and preparation for their organization. Furthermore, microelectrode recordings in monkeys have shown that a large proportion of neurons in the supplementary motor area (which shows reduced activity in PD) contribute to a signal about the order of forthcoming multiple hand movements, suggesting that the supplementary motor area might be involved in planning several movements ahead (Tanji and Shima, 1994). Indeed, Cunnington *et al.* (1997) found that electrophysiological correlates of cortical processing in PD patients are reduced during motor preparation rather than movement execution. The ability of PD patients to perform motor imagery of gait, and its cerebral correlates, could therefore be used to examine which difficulties with motor planning might underlie gait problems in PD (*Chapter* 6). For upper limb movements, motor imagery has already provided useful information about motor planning in PD (Cunnington *et al.*, 2001; Dominey *et al.*, 1995; Helmich *et al.*, 2007; Samuel *et al.*, 2001; Thobois *et al.*, 2000). For example, it was shown that asymmetrically affected PD patients are slower in imagining moving their more affected hand (Dominey *et al.*, 1995; Helmich *et al.*, 2007).

Aim and outline of the thesis

The main aim of the work described in this thesis is using motor imagery to examine the supraspinal control of gait in both healthy subjects and patients with PD.

Chapter 2 provides an overview of the different approaches that have been used to examine the supraspinal control of gait using functional neuroimaging, both in healthy subjects and PD patients. The approaches range from imaging of actual gait performance to the study of initiation and imagery of gait. It describes the methodological issues involved in these different approaches, and provides a critical discussion of the advantages and disadvantages of each approach. The study described in *Chapter* 3 aims at developing a quantitative approach to motor imagery of gait. The goal is to develop an experimental setting in which it is possible to quantify imagery of gait, and to study the neurophysiology of gait. In *Chapters* 4 and 5 the new experimental set-up is used to examine the neural correlates of motor imagery of gait in healthy subjects. In *Chapter* 4, the cerebral correlates of motor imagery of both normal gait and precision gait (walking along a very narrow pathway) are examined using functional magnetic resonance imaging (fMRI). The complementary study in *Chapter* 5 examines whether corticospinal excitability is increased during motor imagery of gait, as examined using transcranial magnetic stimulation (TMS). In *Chapter* 6, motor imagery is used as a tool to investigate neural activity related to planning of gait in PD, again using fMRI as outcome measure. Finally, *Chapter* 7 provides a summary of the main findings and sketches an outlook for further research.

Chapter

C2

Recent advances in functional neuroimaging of gait

This chapter is based on: Bakker M, Verstappen CCP, Bloem BR, Toni I (2007). J Neural Transm, 114(10), 1323-31.

Summary
In this review, we discuss the contribution of functional neuroimaging to the understanding of the cerebral control of gait in humans, both in healthy subjects and in patients with Parkinson's disease. We illustrate different approaches that have been used to address this issue, ranging from the imaging of actual gait performance to the study of initiation and imagery of gait. We also consider related approaches focused on specific aspects of gait, like those addressed by repetitive foot movements. We provide a critical discussion of advantages and disadvantages of each approach, emphasizing crucial issues to be addressed for a better understanding of the neural control of human gait.

Introduction

Most of the existing knowledge about the cerebral control of gait in mammals comes from studies in cats and rodents (Armstrong, 1986; Drew *et al.*, 1996; Rossignol *et al.*, 2006). This work indicates that gait is regulated by cortical and subcortical structures, but it is unclear to what extent these findings can be extended to the voluntary control of human gait. Here we review recent developments on the cerebral bases of gait in humans, developments made possible by using different non-invasive neuroimaging techniques, both in healthy subjects and in clinical populations with gait disturbances.

Neuroimaging of gait is not straightforward. For instance, structural neuroimaging of patients with gait disorders has provided limited insights, given that cerebral lesions causing higher-level gait disorders are typically multiple, or diffuse (Masdeu, 2001). In addition, functional neuroimaging poses practical problems, since techniques like positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) require that subjects do not move their head during the sampling of task-related cerebral activity. These problems have been overcome by developing alternative neuroimaging techniques that allow for recording of cerebral activity during actual gait; by recording cerebral activity during motor planning of walking prior to walking initiation; by using tasks that share some cerebral processes with gait, without the need to engage in actual gait (like motor imagery of gait, or repetitive foot movements); and by recording cerebral activity in patients with gait disorders during rest.

We will discuss how functional neuroimaging has contributed to the understanding of human gait control, in both healthy subjects and – as an example of a common neurodegenerative disease characterized by gait difficulties – patients with Parkinson's disease. We describe the different approaches that have been used and the methodological issues involved in these different approaches (Table 2.1). Our goal is to provide a critical review of the available literature.

Functional neuroimaging of gait in healthy subjects

Gait performance

An obvious approach that has been used to examine the neural control of gait in healthy subjects is to record cerebral activity during physical gait performance. An advantage of this approach is that cerebral activity is directly related to actual walking. However, there are also considerable disadvantages: studying a walking person does not allow for discriminating whether the evoked activity is due to sensory input or motor output, and only a limited number of neuroimaging techniques can be used (because of movement artefacts).

A few neuroimaging techniques are available that can assess cerebral activity during actual gait (see Table 2.1). To date, these involve nuclear neuroimaging techniques, near-infrared spectroscopy (NIRS) and transcranial magnetic stimulation (TMS). Nuclear neuroimaging techniques allow for recording of cerebral activity during gait by separating in time task performance from image acquisition. For example, single photon emission tomography with technetium-99m-hexamethyl-propyleneamine oxime ([^{99m}[Tc]HM-PAO SPECT) records cerebral activity during walking by injecting radioactively labelled HM-PAO during locomotion, and recording cerebral activity afterwards with SPECT. When radioactively labelled HM-PAO is injected intravenously during gait, it is rapidly distributed in the brain in proportion to regional cerebral blood flow and retained in the brain for hours. Therefore, the distribution of HM-PAO at the time of scanning reflects the pattern of cerebral perfusion at the time of injection. Fukuyama *et al.* (1997) used this approach to

Table 2.1 Advantages and disadvantages of available approaches for functional neuroimaging of gait

Approach	Techniques	Advantages	Disadvantages	Used in PD
Gait performance	NIRS, nuclear neuroimaging techniques, TMS	Cerebral activity is directly related to actual walking.	Relatively low spatial resolution. Difficult to discriminate between activity related to planning, execution and the processing of sensory feedback. Difficult to match task performance and task difficulty across groups.	Yes
Gait initiation	EEG	Cerebral activity is directly related to actual gait initiation. High temporal resolution. Minimal confounds from changes in sensory input.	Low spatial resolution. Challenging due to movement artefacts. Difficult to match task performance and task difficulty across groups.	Yes
Motor imagery of gait	NIRS, fMRI, $H_2{}^{15}O$-PET	High spatial resolution. Allows for examining motor planning independent from execution and the processing of sensory feedback. Minimal confounds from movement artefacts.	Evidence for the cerebral overlap between imagery and execution has been mostly obtained from finger and hand movements. Only one study has directly compared imagined and actual gait (Miyai et al., 2001). Difficult to monitor task performance. Difficult to match task performance and task difficulty across groups.	No
Repetitive leg or foot movements	NIRS, fMRI, $H_2{}^{15}O$-PET	High spatial resolution. Allows for examining mechanisms such as internal pacing and interlimb coordination. Allows for comparing active and passive movements.	It remains to be established to what extent the motor control of repetitive foot or leg movements has cerebral analogies with the motor control of gait. Movement artefacts might confound results. Difficult to match task performance and task difficulty across groups.	No
Rest	Nuclear neuroimaging techniques	High spatial resolution. Perfectly matched “performance”. No movement artefacts.	Difficult to match different groups (they should only differ in their gait problems).	Yes

EEG = electroencephalography; fMRI = functional magnetic resonance imaging; NIRS = near-infrared spectroscopy; PD = Parkinson’s disease; PET = positron emission tomography; TMS = transcranial magnetic stimulation;

map cerebral activity during walking and showed that during gait cerebral activity increased in the supplementary motor area (SMA), medial primary sensorimotor area, striatum, cerebellar vermis and visual cortex. This was the first study to show changes in cortical activity during walking in human subjects. A later study by the same group demonstrated that the cerebral activity during walking is not only observed in cortical and subcortical structures, but also in the dorsal brainstem (Hanakawa *et al.*, 1999b). This finding is important, because it is one of the few observations suggesting the presence of brainstem locomotor centres in humans. However, given the limitations of SPECT, gait-related cerebral activity could only be compared with a physical rest condition (lying down with eyes open) in both studies. This raises the issue of whether those cerebral changes are specifically related to gait, over and above changes in somatosensory feedback from the lower limbs between gait and rest.

Another technique that allows for recording of cerebral activity during actual gait is near-infrared spectroscopy (NIRS). NIRS records the transmission and absorption of NIR light by human tissue. The skull does not absorb much infrared light, and therefore NIRS can be used to measure the levels of oxygenated, deoxygenated and total haemoglobin related to neural activity in superficial cortical areas. The optodes of NIR systems are fixed to the skull, and therefore head movements are allowed during measurement. Cerebral activity can be assessed while subjects are walking on a treadmill. NIRS has several advantages compared to HM-PAO SPECT: it does not involve a radioactive tracer, it has a better temporal resolution, and it allows for comparing several conditions. For instance, using NIRS, Miyai *et al.* (2001) were able to compare cerebral activities evoked during gait, alternating foot movements, arm swing, and motor imagery of gait. Gait-related responses along the central sulcus were medial and caudal to activity associated with arm swing, in agreement with the known somatotopic organization of the motor cortex. Crucially, these authors showed that walking increased cerebral activity bilaterally in the medial primary sensori-motor cortices and the SMA, and to a greater extent than the alternation of foot movements. Unfortunately, the spatial distribution and intensity of these responses were not statistically compared. In a different NIRS study, Suzuki *et al.* (2004) examined the effect of different walking speeds on cerebral activity. They demonstrated that cerebral activity in the prefrontal cortex and premotor cortex tended to increase as locomotor speed increased, whereas cerebral activity in the medial sensorimotor cortex was not influenced by locomotor speed. In summary, NIRS has been particularly useful for studying the cortical bases of locomotor control. Unfortunately, given the limited penetration of infrared light (a few centimetres from the skull surface), this technique can only assess the responses of the most superficial portions of the cerebral cortex.

A third technique that has been used to examine the neural substrate of gait during actual walking is transcranial magnetic stimulation (TMS). TMS is a non-invasive method to excite neurons in the brain. If TMS is applied to the primary motor cortex, it can evoke muscle activity which can be recorded using electromyography. TMS has been useful to examine the contribution of the corticospinal tract to the control of gait (see e.g. Camus *et al.*, 2006; Christensen *et al.*, 1999; Petersen *et al.*, 2001; Schubert *et al.*, 1997). However, given that the use of this technique has been circumscribed to the corticospinal tract, we will not discuss it at length.

Gait initiation

Recording of EEG during walking is challenging due to movement artefacts. However, some authors have been able to record electrical activity with scalp electrodes prior to or during gait initiation (do Nascimento *et al.*, 2005; Yazawa *et al.*, 1997). This approach has great advantages, since it provides a direct measure of electrophysiological activity in the brain at high temporal resolution. In addition, there are only minimal confounds of changes in sensory input, because the recording

is performed prior to the onset of movement. For instance, Yazawa *et al.* (1997) examined EEG in a period immediately preceding gait initiation, when subjects had just received an auditory stimulus and were waiting for a second auditory stimulus in response to which they were asked to initiate gait as quickly as possible. They found stronger event-related potentials (contingent negative variation) in the medial central region (Cz) when comparing EEG activity preceding externally-cued gait initiation with activity preceding foot dorsiflexion. This EEG difference indicates that the medial frontal cortex, over and above its role in initiating a simple foot movement, supports the initiation of gait, presumably through the synchronized activity of a large number of dendritic trees (Luck, 2005). However, given the low spatial resolution of this technique, it remains to be seen from which portion of the medial frontal cortex this activity is generated from.

Motor imagery of gait

Given the plethora of technical problems and limitations associated with assessing the cerebral bases of true gait control, several research groups have chosen to focus their efforts on the more tractable aspects. Accordingly, some studies have investigated motor imagery of gait, i.e. the mental simulation of gait without actual execution (Jahn *et al.*, 2004; Malouin *et al.*, 2003; Miyai *et al.*, 2001; Sacco *et al.*, 2006). This approach exploits the documented neural and cognitive overlap between movement planning and motor imagery: imagining a movement relies on neural processes partly similar to those evoked during actual performance of the same movement (Lang *et al.*, 1994; Deiber *et al.*, 1998; Porro *et al.*, 1996; Roth *et al.*, 1996; Stephan *et al.*, 1995). Although most of the evidence for this cerebral overlap between simulation and execution of a movement has been obtained from finger and hand movements, Miyai *et al.* (2001) combined fMRI and NIRS measurements to show a degree of overlap between actual and imagined gait. Using motor imagery to study the cerebral correlates of gait provides considerable practical advantages, since motor imagery does not involve any actual movements, and it can be studied in a recumbent position compatible with techniques like fMRI and PET. This is important, since these techniques provide relatively high spatial resolution and whole-brain coverage. Furthermore, there are also conceptual advantages in using motor imagery. It has been argued that the internal simulation of an action, as evoked during motor imagery, constitutes the core element of a motor plan (Jeannerod, 1994). Furthermore, motor imagery allows one to study cognitive and cerebral properties of movement representations independently from motor output and sensory feedback (de Lange *et al.*, 2005). However, the latter is true insofar subjects are genuinely involved in a motor simulation, i.e. they imagine *themselves* moving, rather than using visual imagery of someone else moving, or visual imagery of the visuospatial processes involved in walking. Given the fact that gait is a learned automatic movement, it might be particularly difficult to voluntarily imagine the movements involved in walking. For instance, when subjects are trained to focus their attention on the movements of their legs by means of basic tango lessons and motor imagery of the performed steps, there is an expansion of activity in the bilateral motor areas, and a reduction of visuospatial activation in the right posterior cerebral cortex during motor imagery of gait performed after this training compared to before the training (Sacco *et al.*, 2006). These findings suggest that focusing subject's attention on the movements involved in walking decreases the role of visual imagery processes in favour of motor-kinaesthetic ones. Therefore, when using motor imagery to study gait, it becomes particularly important to use tasks that are designed to evoke first-person kinaesthetic imagery and that allow for monitoring subjects' performance and prove their engagement in kinaesthetic motor imagery (Jeannerod, 1994).

Motor imagery of gait has been examined using NIRS, fMRI and $H_2{}^{15}O$-PET (see Table 2.1). Malouin et al (2003) used $H_2{}^{15}O$-PET to compare cerebral activity evoked during motor imagery of standing, initiating gait, walking, and walking with obstacles. Prior to the experiment, subjects were

shown a video of each imagery condition. The video was taken from a first person perspective to facilitate first person motor imagery and to standardize imagined walking speed. During PET scans, subjects were asked to imagine the different movements, from a first person perspective and with their eyes closed. Motor imagery of walking increased cerebral activity in the pre-SMA when compared to imagined standing, and in the left visual cortex and caudate nucleus when compared to imagery of gait initiation. Motor imagery of walking with obstacles increased cerebral activity in the precuneus bilaterally, the left SMA, the right parietal inferior cortex and the left parahippocampal gyrus compared to motor imagery of walking without obstacles. These results are important, since they are the first to illustrate that the circuitry supporting gait can extend beyond core motor regions, and it can be modulated by the difficulty of the (imagined) locomotor task. Prior to scanning, imagery performance was monitored using a chronometry test and a questionnaire, which both suggested that subjects were able to perform motor imagery. However, during scanning imagery performance was monitored through its effect on heart rate, and this parameter cannot easily determine whether subjects were able to adequately perform motor imagery.

In another study, Jahn et al (2004) compared cerebral activity during motor imagery of standing, walking and running using fMRI. To induce first person motor imagery and to standardize motor imagery performance, subjects were trained to perform the actual movements on a basement floor prior to the imagery experiment. During motor imagery, subjects closed their eyes and imagined performing the same movements from a first person perspective. However, there was no behavioural quantification of imagery performance. Cerebellar activation increased during motor imagery of running but not during motor imagery of walking and standing. Vestibular and somatosensory cortex were deactivated during running but not during walking. These findings suggest that speed of gait is under the control of a cerebellar locomotor centre, and that cortical processing of vestibular and somatosensory information is particularly important during walking. Unfortunately, the between-tasks differences in cerebral activity were not formally tested, thus no clear inference can be drawn about the involvement of these structures in the different locomotor tasks.

Repetitive leg or foot movements

A further approach to asses the cerebral bases of gait control is to examine repetitive leg or foot movements, as a surrogate for gait. The rationale is that these movements are thought to rely on partly similar neural processes as those used during walking. For example, alternating foot flexion-extension movements and bicycling movements require internal pacing and interlimb coordination, mechanisms that are also required during gait. Miyai *et al.* (2001) combined NIRS and fMRI and showed that foot-extension flexion movements indeed generate a similar brain activation pattern to that associated with walking. Using foot or leg movements to study the cerebral correlates of gait provides considerable practical advantages, since these movements can be performed with minimal movements of the head, and in a recumbent position. Another advantage is that voluntary foot or leg movements can be matched with similar passive movements, and this procedure allows one to dissociate responses to somatosensory input from the volitional aspects of the task (Mima *et al.*, 1999). However, the relationship between lower limb movements and gait is limited. Leg or foot movements do not allow for examining the way in which several important features of gait (such as the upright stance, truncal control and co-innervation of gluteal and leg muscles) are controlled. Therefore, it remains to be established to what extent the motor control of repetitive foot or leg movements has cerebral analogies with the motor control of gait.

Repetitive foot movements have been investigated using NIRS, fMRI and $H_2{}^{15}O$ PET (see Table 2.1). The group of Sahyoun (2004) used fMRI to compare active versus passive unilateral foot extension-flexion movements and found that cerebral activity increased in the somatosensory

cortex, SMA, cingulate motor area, secondary somatosensory cortex, insular cortices, putamen, thalamus and cerebellum during active compared to passive foot movements. This suggests that both cortical and subcortical structures are involved in the motor control of rhythmic foot movements. In another study, de Jong *et al.* (2002) examined cerebral activity during antiphase flexion and extension movements of the two upper and the two lower limbs using $H_2{}^{15}O$ PET. They hypothesized that a common neural circuitry would be involved in antiphase movement, independently of whether they would be performed with the two upper or lower limbs. For both the arms and legs, cerebral activations related to antiphase movements were distributed over the right anterior parietal and right dorsal premotor cortex, suggesting that these structures support the sensorimotor integration required for antiphase movements. However, it is important to realize that controlling flexion-extensions of the foot is much simpler than controlling gait. For example, gait involves the coordination between a large number of body parts, and the integration of vestibular, visual, and somatosensory signals. A particularly delicate element of gait is the precise inter-limb timing (Plotnik *et al.*, 2005), and this will be difficult to mimic using repetitive foot movements, even when performed alternatingly in both feet.

The issue of inter-limb timing can perhaps be addressed by studying bicycle movements. Indeed, (Christensen *et al.*, 2000) used such bicycle movements to exactly matched active and passive movements, while addressing inter-limb coordination. Muscle activity during human bicycling is very similar to that during locomotion and is also often assumed to be generated by a similar central network (Raasch and Zajac, 1999). Using $H_2{}^{15}O$ PET, Christensen *et al.* (2000) found that both passive and active bicycling increased cerebral activity bilaterally in primary sensorimotor cortices, SMA, and the anterior part of the cerebellum. When passive bicycling was subtracted from active bicycling, significant activation was found in the leg area of the primary motor cortex and the precuneus. These findings suggest that there is a significant cerebral involvement in the motor control of rhythmic motor tasks such as bicycling. However, given that it was quite difficult for subjects to remain absolutely relaxed during passive bicycle movement, some of the activity observed during the passive movements might be due to unwanted muscular activity. More importantly, it is unlikely that the cerebral network involved in the motor control of bicycling is confined to the primary motor cortex and precuneus.

Functional neuroimaging of gait in Parkinson's disease

Insufficient knowledge of underlying gait mechanisms not only exists for healthy subjects, but also for patients with gait disturbances of a central neural origin, like patients with Parkinson's disease (PD). Gait disturbance in PD is thought to originate, at least in part, from nigrostriatal dopamine deficiency, that in turn alters the basal ganglia-brainstem circuits and the basal ganglia-thalamocortical systems (Bloem *et al.*, 2004). The precise pathophysiological mechanism, however, needs to be elucidated.

Gait performance in PD

A first approach that has been used to examine the neural control of gait in patients with PD is to measure cerebral activity during gait performance and to compare it with that measured during gait performance of healthy subjects. An advantage of this approach is that cerebral activity is directly related to gait performance. However, this advantage should be weighted against the intricacies of matching both performance and task difficulty across patients and control groups.

Actual gait in PD has been investigated using HM-PAO SPECT and DAT-PET. The group of Hanakawa *et al.* (1999b) has described two studies using HM-PAO-SPECT comparing regional cerebral blood flow during treadmill walking. In the first study, they compared mildly to moder-

ately impaired PD patients with age-matched healthy controls, while walking at the same speed on a treadmill. The PD patients showed a relative decrease in brain activity in the left medial frontal lobe, right precuneus and left cerebellar hemisphere. In contrast there was an increased cerebral blood flow in the cerebellar vermis, right insula, left temporal cortex and left cingulate gyrus. The reduced brain perfusion in the frontal motor areas fits with similar results obtained during arm and finger movements (Berardelli *et al.*, 2001), pointing to a systematic alteration of activity in this region during motor performance in PD patients. The authors suggest that the overactivity in the cerebellar vermis in combination with an underactivity in the cerebellar hemisphere might be associated with a loss of lateral gravity shift in PD.

The same group performed a follow-up study, investigating the effects of visual cuing on gait in PD patients. It is known that visual cues can help PD patients to overcome gait disturbances, especially freezing (Bloem *et al.*, 2004). Accordingly, Hanakawa and colleagues (1999a) applied transverse or parallel white lines to the walking surface of a treadmill. Gait abnormality in PD patients was ameliorated in the transverse line situation. The authors compared brain activity evoked during gait in the transverse line condition and in the parallel line condition. In both controls and PD patients, there were increased responses in the posterior parietal cortex and cerebellar hemispheres during gait in the transverse line condition. Crucially, the premotor area activation was significantly greater for PD patients than for controls, suggesting that this region may be involved in visuomotor control of gait in patients with a "paradoxical" (externally cued) gait. However, it remains unclear whether these results were influenced by residual difference in performance between the two groups. Despite the use of a treadmill, task performance was not completely matched between patients and controls. More generally, one might wonder whether cerebral activity associated with the forced locomotion evoked on a treadmill is comparable to that evoked during spontaneous gait, or to parkinsonian gait.

It might be argued that a meaningful approach to the cerebral correlates of gait disturbances in PD patients should directly consider the modulatory effects of dopaminergic activity in the basal ganglia on the motor system. Accordingly, Ouchi *et al.* (2001) investigated changes in dopamine transporter (DAT) availability during standing and during gait in unmedicated PD patients and in normal subjects. Subjects underwent two serial PET scans ([^{11}C]CFT-PET). The second scan was performed after tracer injection and a subsequent walk of 50 minutes. Participants walked at their own pace along a white line in the corridor back and forth. Normal subjects were requested to walk more slowly. Stride length and cadence were not significantly different between PD patients and controls. The latter group showed a significant reduction of [^{11}C]CFT uptake during gait in both the putamen and in the caudate. PD patients showed a similar reduction of [^{11}C]CFT uptake in the caudate (and orbitofrontal cortex), but not in the putamen. This study points to alterations in the availability of DAT in the medial striatum as a source of pathophysiological changes in gait performance in PD patients. However, the specificity of these effects remains to be tested, given that changes in local regional blood flow during exercise may affect levels of tracer binding. Furthermore, PD patients showed difficulties while turning at each end of the corridor, suggesting that there might have been residual differences in task difficulty between patients and controls.

Gait initiation in PD

One study by the group of Vidailhet has investigated the initiation of gait in PD by means of the Bereitschaftspotential (BP) using EEG (Vidailhet *et al.*, 1993). The BP is a movement-related potential, with two main components; an early one (BP1) lasting from about 1.2 to 0.5 sec before movement onset, and a late component (BP2) shortly (0.5 sec) before movement onset (Deecke *et al.*, 1976). The BP is an electrical sign of participation of the SMA prior to volitional movement

(Deecke and Kornhuber, 1978). Vidailhet *et al.* (1993) found that PD patients showed little change in either early or late components of the BP between foot dorsiflexion and stepping tasks. In contrast, controls subjects showed a larger peak in the early BP phase before a stepping movement than preceding a voluntary dorsiflexion. Distribution of the BP was most conspicuous over midline scalp positions (Fz, Cz), but also ipsilaterally (P4, posterior parietal) to the foot movement (Vidailhet *et al.*, 1993). The altered activity over medial frontal motor areas fits the imaging results obtained during actual gait (Hanakawa *et al.*, 1999b), emphasizing that PD patients have altered motor planning activity well in advance of gait execution.

Baseline perfusion in PD

Under the assumption that pathological alterations in brain activity are likely to be present not only during task performance but also during rest, some authors have examined baseline cerebral perfusion to investigate the cerebral bases of altered neural correlates of gait control in PD patients. This approach has the considerable advantage of perfectly matched "performance" across different subject groups. However, when using this approach to compare gait problems between two different groups of subjects, it is important to closely match the different groups. In the ideal situation, the only difference between the different subject groups would be their gait problems, and this is difficult to achieve in practice where gait is closely related to other relevant variables such as disease severity and disease duration. In PD, baseline perfusion has been used to examine freezing problems in patients with Parkinson's disease, and to examine the effects of gait training.

Freezing of gait is a unique and extremely debilitating symptom of PD, with an unknown pathophysiological mechanism. There have been a few studies that tried to localize the altered cerebral activity associated with freezing. Using ^{123}I-IMP-SPECT, Matsui *et al.* (2005) compared cerebral activity in PD patients with and without freezing, at comparable clinical stages of the disease. SPECT scanning was performed in a supine condition, at rest. Perfusion of the orbitofrontal area (Brodmann area 11) in the freezing of gait group was decreased, as compared to the non-freezing group. Another study has addressed this issue, but Fabre *et al.* (1998), using ^{133}Xenon-SPECT in patients with PD and severe "off" freezing, could not find any specific effect in the orbitofrontal area. Finally, Bartels *et al.* (2006) addressed this issue using better spatial resolution than the previous studies. FDG-PET and 18[F]-6-fluoro-levodopa (FDOPA)-PET was used to compare striatum decarboxylase activity in two groups of PD patients with and without freezing of gait. Lower putaminal FDOPA uptake with increased FDG uptake was observed in freezing PD patients, whereas caudate uptake of both FDG and FDOPA was reduced. Furthermore, in freezing patients a decreased FDG uptake was found in the parietal cortices. This last study, although using a different technique, did not show differences in the frontal lobe compared to the other two studies. Taken together, these studies suggest that medial frontal and basal ganglia might be altered in PD patients with freezing of gait, but at the moment the consistency of the results prevents any clear inference.

Finally, imaging techniques have been recently used to assess the effect of a gait rehabilitation program in PD patients. Del Olmo *et al.* (2006) recorded baseline cerebral perfusion with 2-deoxy-2[^{18}F]fluoro-D-glucose-PET (FDG-PET) in PD patients that walked with or without rhythmic auditory cues. The measurements were made before and after four weeks of a rehabilitation program based on auditory cues, aimed at minimizing the temporal variability of gait. The rationale for using this program was that PD patients depend strongly on external cues, both visual and auditory, to initiate or maintain walking. Before therapy, PD patients showed a significant hypometabolism in the right parietal lobe, temporal lobes, and left frontal lobe. Hypermetabolism was found in the left cerebellum. After therapy a significant increment of metabolism was found in the right cerebellum, right parietal lobe and temporal lobes, combined with a decrement of temporal variability during

gait. This study shows training-related changes both in behaviour and cerebral glucose metabolism. However, it remains to be seen whether the cerebral changes are specifically related with clinical improvements across a large number of patients.

Conclusion

In this review we have illustrated how functional neuroimaging techniques have been used to obtain information about the cerebral bases of gait control in healthy subjects, and about gait disturbances in patients with PD. Taken together, these studies have shown that the medial aspect of the motor cortex, controlling the lower limbs, can be modulated by different portions of the motor system, from posterior parietal cortex to the basal ganglia and the cerebellum. The basal ganglia-thalamo-cortical system presumably plays a major role in gait disorders in patients with PD.

In the clinical domain, given that several aspects of gait disturbances seem to be related to motor planning and rhythmic pacing, rather than motor execution per se, it appears reasonable to use motor imagery of gait and repetitive foot movements in patients with disorders such as PD. Using these approaches might also open the possibility to use other techniques, like magnetoencephalography (MEG) and TMS, which provide direct measures of neural activity at high temporal resolution. More importantly, these techniques would allow one to investigate cerebral *circuits* supporting gait, rather than a collection of brain regions showing altered metabolism related to gait. The time seems ripe for assembling these scattered observations into a coherent computational model of gait control in humans, able to generate testable predictions.

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Chapter

C3

Motor imagery of gait: a quantitative approach

This chapter is based on: Bakker M, de Lange FP, Stevens JA, Toni I, Bloem BR (2007). Exp Brain Res, 179(3), 497-504.

Summary
Recently a few studies have used motor imagery tasks to explore the neurophysiology of human gait, but it remains unclear how to ascertain whether subjects actually perform imagery of gait as requested. Here we describe a new experimental protocol to quantify imagery of gait, by behaviourally distinguishing it from visual imagery processes and by showing its temporal correspondence with actual gait. Fourteen young healthy subjects performed two imagery tasks and an actual walking task. During both imagery tasks subjects faced a computer screen that presented photographs of walking trajectories. During one task (motor imagery: MI), subjects had to imagine walking along the walking trajectory. During the other task (visual imagery: VI), subjects had to imagine seeing a disc moving along the walking trajectory. During the actual walking task (AW), subjects had to physically walk along the same walking trajectory as presented on the photographs during the imagery tasks. We manipulated movement distance by changing the length of the walking trajectory, and movement difficulty by changing the width of the walking trajectory. Subjects reported onset and offset of both actual and imagined movements with a button press. The time between the two button presses was taken as the imagined or actual movement time. Movement time increased with increasing path length and decreasing path width in all three tasks. Crucially, the effect of path width on movement time was significantly stronger during MI and AW than during VI. The results demonstrate a high temporal correspondence between imagined and actual walking, suggesting that motor imagery taps into similar cerebral resources as those used during actual gait. These results open the possibility of using this protocol for exploring neurophysiological correlates of gait control in humans.

Introduction

Motor imagery has been defined as mentally simulating a given action without actual execution (Jeannerod, 1994). It has been shown that imagining a movement relies on neural processes similar to those evoked during real performance of the same movement (Lang *et al.*, 1994; Deiber *et al.*, 1998; Porro *et al.*, 1996; Roth *et al.*, 1996; Stephan *et al.*, 1995). Accordingly, motor imagery allows one to identify cognitive and cerebral properties of movement representations independently from motor output and sensory feedback (de Lange *et al.*, 2005). However, this strength might become a weakness when the experimental design does not allow for a quantification of imagery performance. This issue appears to be particularly relevant for imagery studies dealing with the neurophysiology of human gait (Jahn *et al.*, 2004; Malouin *et al.*, 2003; Miyai *et al.*, 2001). Differently from the extensive work done on imagery of hand and arm movements (Decety and Michel, 1989; Johnson-Frey, 2004; Parsons, 1987; Parsons, 1994), it remains unclear how to ascertain whether subjects actually perform imagery of gait. The issues of task compliance and performance are particularly important when studying patient populations. Accordingly, in this study we aim at developing a quantitative approach to motor imagery of gait. Our goal is to have an experimental setting in which it is possible to quantify imagery of gait, and to study the neurophysiology of gait in patient populations without the potential confounds of altered motor output or sensory input. One approach that has been used to quantify task performance during an imagery task involves the use of mental chronometry (Guillot and Collet, 2005). Mental chronometry refers to inferring the time course of information processing in the nervous system (Donders, 1969). It has been demonstrated that a close temporal correspondence exists between actual and imagined movements. For example, it takes approximately the same time to write or to imagine writing a short sentence (Decety and Michel, 1989). In addition, it has been demonstrated that both true and imagined movements conform to Fitts' Law (Decety and Michel, 1989). This law, originally obtained in the context of manual aiming movements (Fitts, 1954), describes the inverse and logarithmic relationship that link the difficulty of a movement and the speed with which the movement can be performed. For instance, when target size decreases during a manual pointing task, movement difficulty increases, and movement speed decreases (Sirigu *et al.*, 1996). Because of the close temporal correspondence between true and imagined movements, imagined movement times have been used to monitor task performance. A close temporal correspondence would suggest that subjects were able to perform the motor imagery task. However, it should be noted, that there continues to be some opposition to the notion that imagined movement times can serve as proof that subjects performed the task. It has been argued that the close temporal correspondence may be attributable to a subject's tacit knowledge about the time it takes to actually execute the movement (Pylyshyn, 2002).

In this study we capitalize and elaborate on recent reports showing that both actual and imagined walking conforms to Fitts' law (Decety, 1991; Decety and Jeannerod, 1995; Stevens, 2005). In these studies, subjects were asked to walk or to imagine walking towards a certain spatial target. Movement distance was manipulated by positioning the target at different distances from the subjects. Movement difficulty was manipulated by asking subjects to walk along beams of different widths (Decety, 1991; Stevens, 2005), or towards doors of different widths (Decety and Jeannerod, 1995). These studies showed that, during performance of both real and imagined movements, walking times increased with increasing movement distance and difficulty. However, it remains unclear how to use these insights in an experimental setting that would allow one to study not only behavioural responses, but also neurophysiological variables. For example, the study of Stevens *et al.* (2005) used a single trial procedure in an ecologically valid environment; that is, during the imagery trial the subject was physically standing in front of the same path used for the walking trial. This task feature might be crucial, as it may be difficult to adequately estimate distance and width of a

walking trajectory from a two-dimensional display. On the other hand, the experimental set-up of Stevens *et al.* (2005) is not immediately compatible with the experimental constraints (averaging over multiple trials, impoverished experimental environment) that are imposed when measuring neurophysiological variables, like functional Magnetic Resonance Imaging (fMRI) or transcranial magnetic stimulation (TMS) experiments. Decety and Jeannerod (1995) circumvented some of these problems by having subjects immersed in a virtual reality environment, but it remains unclear whether such an experience is crucial for evoking motor imagery. Accordingly, we have elaborated on the study of Stevens *et al.* (2005) and adapted it to a neuroimaging setting. In this report we describe this new experimental protocol, and we examine whether we can replicate the behavioural finding described in Stevens *et al.* (2005).

Methods

Fourteen healthy right-handed subjects (7 men; age 22±2.8 years, mean ± SD) participated after giving written informed consent according to institutional guidelines of the local ethics committee.

Experimental settings

There were three linoleum gait trajectories (length = 12 m; thickness = 3 mm). Each trajectory (or path) had a different width (PATH WIDTH: 9, 18, and 27 cm). The path width of 27 cm allowed subjects to easily walk over the path with a normal gait (Fig. 3.1). The path width of 18 cm forced subjects to carefully walk over the path, given the narrow base of support. The path width of 9 cm forced the subjects to walk even more carefully over the path, given the very narrow base of support which approximately equalled the width of a single foot. The beginning of the walking trajectory was marked by a green square (64 cm^2). The end of the walking trajectory was marked by a green pillar (diameter: 7.5 cm, width: 12 cm) which could be placed at 5 different distances from the green square along the path (PATH LENGTH: 2, 4, 6, 8 and 10 m). We made photographs of each of the different walking trajectories (3 path widths x 5 path lengths = 15 walking trajectories - Fig. 3.1A). In addition, we made photographs of each walking trajectory with a black disc (diameter: 7.5 cm, width: 2.5 cm) replacing the green square at the beginning of the walking trajectory (Fig 3.1). This resulted in a total of 30 photographs. Stimuli presentation and behavioural response were controlled through a PC running Presentation software (Neurobehavioral systems, Albany, USA).

Tasks

There were two experimental sessions, an imagery session and an actual walking session. During the imagery session subjects performed two imagery tasks: motor imagery (MI) and visual imagery (VI). During both imagery tasks, subjects were sitting on a chair, facing a computer screen positioned at a distance of 65 cm. Each trial started with the presentation of a photograph of a walking trajectory. During MI trials, a green square was present at the beginning of the path (Fig. 3.1), and subjects had to imagine walking along the path. During VI trials, a black disc was present at the beginning of the path (Fig 3.1), and subjects had to imagine seeing the disc moving along the path. The trial time course for both MI and VI trials was as follows. Subjects could inspect the photograph on display, for as long as they wanted, then closed their eyes and imagined standing next to the green square (MI trials) or the black disk (VI trials) at the beginning of the path. They were then instructed to press a mouse button with the index finger of their right hand to signal that they had started the imagery trial, i.e. they imagined stepping onto the path and walking along the path (MI trials), or imagined seeing the disc moving along the path (VI trials). The subjects were then instructed to press the mouse button again when they imagined that they had reached the end of the walking trajectory (MI trials), or that the disc had reached the end of the walking trajectory (VI trials). During both tasks the end of the walking trajectory was marked by a green pillar.

After subjects had pressed the button they opened their eyes and a fixation cross was presented on the screen until the onset of the next trial (inter-trial interval: 1-2.5 sec). Subjects performed both imagery tasks with their eyes closed, and the time between the two button presses was taken as movement time.

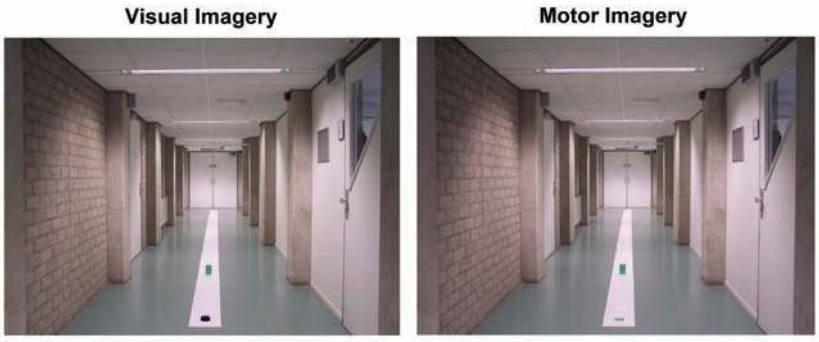

Figure 3.1 Stimuli. *Examples of photographs of walking trajectories presented to the subjects during the motor imagery (MI), and visual imagery (VI) experiment. The photos show a corridor with a white path in the middle and a green pillar positioned on the path. During MI trials, a green square is present at the beginning of the path. During VI trials, a black disc is present at the beginning of the path. During both tasks, the path width can be either: 27 cm, 18 cm, or 9 cm (27 cm in the photos presented in this figure). In addition, the green pillar can be positioned at 2, 4, 6, 8 or 10 m from the green square or black disc (2 m in the photos presented in this figure).*

Subjects performed the two imagery tasks in separate blocks; block order was counter-balanced across subjects. Each condition [i.e., PATH WIDTH (3 levels) and PATH LENGTH (5 levels)] was repeated 6 times, generating a total of 90 trials in each block, with a pseudo-randomized trial order. The imagery session was preceded by an induction phase, in which we presented subjects the three actual paths. Subjects were instructed to pay attention to the width and length of the paths, but were not allowed to walk along them. Instead subjects were asked to walk three times along short versions (2 m) of each of the three path widths, prior to the MI block. This was done to make subjects familiar with the feeling of walking along each of the different path widths. A drawback of this actual walking experience is that it gives subjects tacit knowledge about the time it takes to walk along the different paths, which they might use to solve the imagery task. We used short versions of each of the paths to minimize this problem as much as possible. Subjects were instructed to walk along the paths at a comfortable pace, and they were instructed not to place their feet outside the path. Subjects were explicitly instructed to imagine walking along the paths in a first person perspective, and to imagine as if their own legs were moving. In addition, they were instructed not to make any actual movements. Prior to the VI block, subjects were familiarized with the disc used in the VI trials, and they were informed that the disc moved autonomously, in a straight line and could not move outside the path.

After the imagery session, subjects performed the actual walking (AW) session. The actual walking session was always performed after the imagery session to minimize the amount of tacit knowledge about the time it takes to actually walk along the walking trajectories during the motor imagery

task. During the AW session, subjects physically walked barefoot along the same paths displayed during the imagery session. The subjects were instructed to walk at a comfortable pace, and they were instructed not to place their feet outside the path. Each condition [i.e., PATH WIDTH (3 levels) and PATH LENGTH (5 levels)] was repeated two times, generating a total of 30 trials, with a pseudo-randomized trial order. Each trial started with the subject standing next to a green square placed at the beginning of the path (Fig. 3.1). Then, they were instructed to step onto the path and to walk along the path until they reached the green pillar marking the end of the walking trajectory. As the subjects began and ended the movement, they started and stopped a stopwatch held in their hand. The experimenter recorded the time (movement time). The subjects did not see the recorded movement times during the experiment.

Data analysis

We investigated the effect of TASK (AW, MI, VI), PATH LENGTH (2, 4, 6, 8, 10 m), and PATH WIDTH (9, 18, and 27 cm) on movement time. We also looked at effects of task ORDER (MI-VI-AW, VI-MI-AW) to investigate possible carry-over effects from one task to the next. The significance of the experimental factors was tested within the framework of the General Linear Model using a 3 × 5 × 3 × 2 repeated measures ANOVA. When interactions were significant, the simple main effects were investigated by additional repeated measures ANOVAs. The alpha-level of all behavioural analyses was set at $p < 0.05$, univariate approach. Greenhouse-Geisser corrections were applied to ensure that the assumption of sphericity was met, resulting in adjusted P-values based on adjusted degrees of freedom. Adjusted P-values are given in the results section. In addition, we examined whether movement time obtained in each task conformed to Fitts' law:

Movement time = $a + b \log_2$(2* PATH LENGTH / PATH WIDTH).

In the equation, a and b are constants. The term $\log_2$(2* PATH LENGTH / PATH WIDTH) is called the index of difficulty (ID). It describes the difficulty of the motor tasks. We calculated ID for each of our 15 experimental conditions [i.e., PATH WIDTH (3 levels) and PATH LENGTH (5 levels)]. Several of the conditions had the same ID value. For each task and each subject, the movement time of these conditions was averaged. Fitts' Law states that movement time increases linearly with increasing ID. We therefore examined how well movement time conformed to Fitts' Law by calculating the linear regression of movement time over ID for each task and for each subject separately. Finally, we examined whether the degree to which movement time conformed to Fitts' Law was different for the different tasks, by considering the effect of TASK (AW, MI, and VI) on r^2 after z-score transformation using a repeated measures ANOVA.

Results

We found no significant differences in movement times between the three tasks (TASK: $F(2,24) = 1.1$, $p=0.356$ - Fig. 3.2A). In all three tasks, movement time increased with increasing path length (main effect of PATH LENGTH: $F(1.1,12.9) = 93.02$, $p< 0.001$; MI ($F(1.0,12.5) = 30.0$, $p<0.001$); VI ($F(1.2,14.0) = 32.3$, $p<0.001$); AW ($F(1.3,15.8) = 1297.4$, $p<0.001$) - Fig. 3.2B), and with decreasing path width (main effect of PATH WIDTH: $F(1.1,13.3) = 28.4$, $p< 0.01$: - Fig 3.2C). However, the effect of path width on movement time differed for the different tasks (TASK x PATH WIDTH interaction: $F(2.2,26.5) = 3.8$, $p= 0.032$). The effect of path width was greater for AW than for VI ($F(1.2,13.8) = 4.9$, $p=0.040$), and for MI than for VI ($F(1.3,15.5) = 6.5$ $p=0.016$), and it was not significantly different between MI and AW ($F(1.1,13.4) = 0.4$, $p=0.578$). Additional analysis demonstrated that movement time significantly increased with decreasing path width during both MI ($F(1.1,13.5) = 16.4$, $p=0.001$) and AW ($F(1.1,12.8) = 34.3$, $p<0.001$), whereas there was a trend that movement time increased with decreasing path width during VI ($F(1.2,14.2) = 4.2$, $p=0.054$).

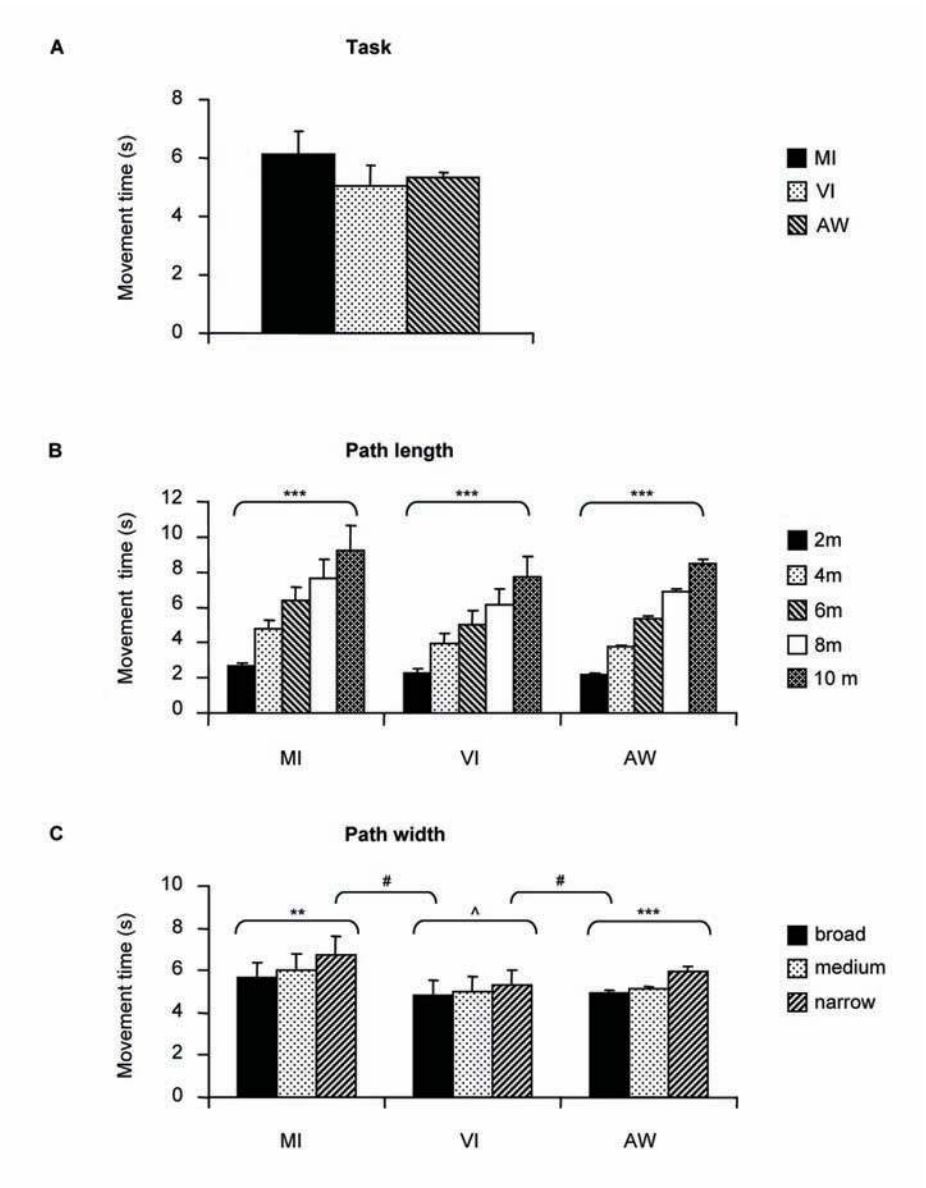

Figure 3.2 Behavioural results. *Movement times are shown for* ***A)*** *each of the three tasks (motor imagery (MI), visual imagery (VI) and actual walking (AW),* ***B)*** *for the five different path lengths (2, 4, 6, 8, and 10 m) separately for each task, and* ***C)*** *for the three different path widths (broad (27 cm), medium (18 cm) and narrow (9 cm)) separately for each task. Data represent mean +/- SEM. *** P<0.001, ** P<0.01, ^ P=0.054 (Effects of path length and path width on movement time for each task separately), # P<0.05 (Differential effect of path width on movement time across the different tasks).*

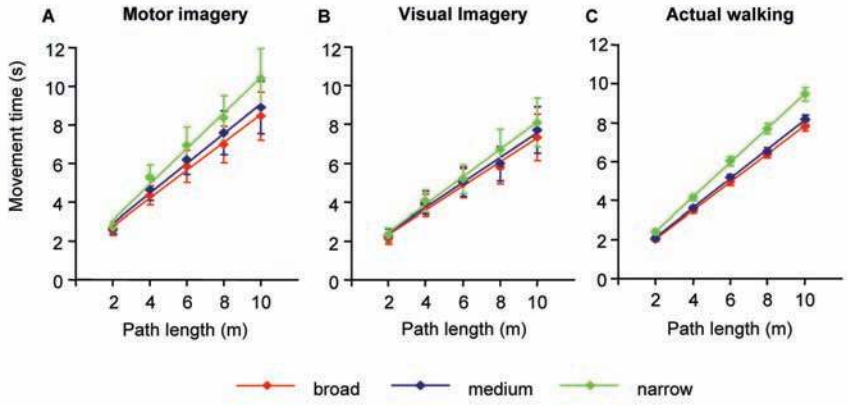

Figure 3.3 Behavioural results. *Movement times are shown separately for five different path lengths (2, 4, 6, 8 and 10 m) and 3 different path widths (broad (27 cm), medium (18 cm) and narrow (9 cm)), for* ***A)*** *motor imagery (MI),* ***B)*** *visual imagery (VI), and* ***C)*** *actual walking (AW). Data represent mean +/- SEM.*

The effect of path width on movement time was not influenced by the order in which the different tasks were performed (PATH WIDTH x ORDER interaction: $F(1.1,13.3) = 1.0$, $p= 0.388$; TASK x PATH WIDTH x ORDER interaction: $F(2.2,26.5) = 0.3$, $p= 0.743$). The effect of path width on movement time differed for the different path lengths (PATH WIDTH x PATH LENGTH interaction: $F(2.6,31.0) = 17.6$, $p< 0.001$), such that the effect of path width increased with increasing distance (Fig. 3.3).

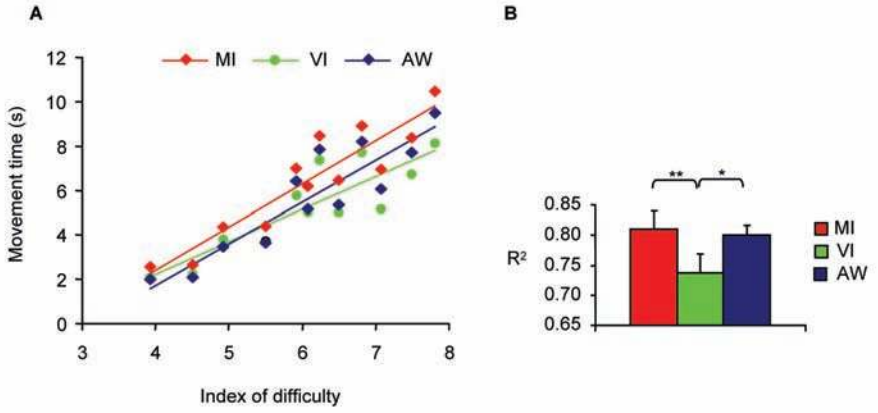

Figure 3.4 Fitts' law. A) *Average movement times plotted against the index of task difficulty (ID) for motor imagery (MI), visual imagery (VI) and actual walking (AW). ID is calculated for each condition with the following formula: log2(2* PATH LENGTH / PATH WIDTH). Dashed lines represent regression curves between movement time and ID.* ***B)*** *Average R^2 of the correlation between movement time and ID for each of the different tasks. * P<0.05, ** P<0.01 (Post hoc comparison of R^2 across the different tasks).*

Movement time correlated linearly with ID in each of the three tasks (Fig. 3.4A). However, the r^2 of this correlation was different for the different tasks (main effect of TASK: $F(2.26) = 6.1$, $p=0.007$) - Fig 3.4B) . The r^2 was greater for MI than for VI ($F(1,13) = 12.8$, $p=0.003$), and for AW than for VI ($F(1,13) = 6.0$, $p=0.029$), but the r^2 did not differ between MI and AW ($F(1,13) = 0.1$, $p=0.798$).

Discussion

This study describes a new experimental protocol for studying and quantifying motor imagery of gait in a neuroimaging environment. This protocol allows one to behaviourally distinguish motor imagery of gait from visual imagery. Furthermore, under these circumstances, we found a tight behavioural correspondence between imagined and actual gait. There were two main findings. First, movement time increased with increasing path length and decreasing path width in all three tasks. Second, the effect of path width on movement time was significantly stronger during MI and AW than during VI. The results demonstrate that movement time is equally sensitive to path length and path width during both actual and imagined gait performance, suggesting that subjects complied with the motor imagery task. The stronger effect of path width during MI and ME than during VI suggests that this protocol allows one to behaviourally distinguish between MI and VI.

There was a close temporal relationship between actual and imagined walking. This finding suggests that subjects were able to preserve the temporal organization of gait during motor imagery of gait, performed in the new setting. This result is not trivial since no previous study has examined the temporal relationship between actual and imagined gait while actual gait is performed in a real environment and imagined gait is performed while sitting on a chair and facing a computer screen presenting photographs of the same environment. Our results demonstrate that the two-dimensional photographs provided sufficient and relevant information about the length and the width of the walking trajectories, and that subjects were able to imagine walking in an environment in which they were not actually present. Another new aspect of this study is that we demonstrated that actual and imagined walking evoked similar movement times across a relatively large number of trials. This finding indicates that it is possible to obtain a stable and functionally relevant performance even across multiple trials, a necessary requirement for using this experimental protocol in the context of noisy neurophysiological measurements like fMRI or TMS that rely on multiple-trial averaging.

In the study of Stevens *et al.* (2005), imagined walking times were shorter than actual walking times. Here, we found no significant differences in movement times between MI and AW. This discrepancy is likely due to differences in the instructions given to the subjects. Stevens instructed subjects to imagine walking as fast as possible, whereas we asked the subjects to walk at a natural pace. We used these instructions in order to test the validity of our settings during performance and imagery of gait at a natural speed, and with the further goal of using this setting in neurological populations. More generally, this result illustrates that, during tasks that explicitly require the subjects to engage in mental imagery, task instructions influence the assumptions and beliefs the subjects use to solve the task at hand (Pylyshyn, 2002). Other implicit imagery tasks (Johnson-Frey, 2004; Parsons, 1987; Parsons, 1994) might be less prone to this effect.

The differential effect of path width during VI compared to MI and ME indicates that this protocol allows one to obtain behavioural indexes to distinguish between motor imagery and visual imagery. The distinction between MI and VI was however less pronounced than observed by Stevens *et al.* (2005). Whereas Stevens found no effect of path width on movement time during VI, we found a trend that movement time increased with decreasing path width during VI. There

are several possible explanations for this discrepancy. One possible explanation could be that MI experience influenced VI in our experiment. In the study by Stevens *et al.* (2005) MI and VI were performed by two different groups of subjects, whereas in our experiment all subjects performed both tasks. Therefore MI experience might have influenced VI performance in our study. However, the order of the motor and visual imagery task was randomized across subjects, and the effect of path width on movement times during VI was the same when VI preceded or followed MI. Differences in task instructions might be a more likely explanation. Stevens instructed subjects to imagine seeing the disc moving "as fast as possible", and she found that movement times were smaller during VI than during MI. In contrast, we did not specify the speed of the moving disc, in order to avoid overall differences in movement times between MI and VI. We tried to avoid these overall differences since they might be considered a source of confounds in the context of neuroimaging experiments (Wilkinson and Halligan, 2004). However, by not giving subjects any information about the speed of the moving disc, in combination with explicitly instructing subjects to pay attention to the different path widths, some subjects may have reasoned that the disc movement would be influenced by the path width. For example, subjects may have imagined some motoric agent causing the movement of the disc. We tried to prevent this by specifically instructing subjects to imagine seeing the disc moving autonomously. However, we cannot exclude the possibility that some subjects imagined a motoric agent influencing the movement of the disc. In a follow-up imaging study, we have addressed this issue by showing a video of the disc moving autonomously at constant speed through the corridor prior to the experiment. We found this procedure to considerably reduce the effect of path width on movement times in the VI trials (Bakker *et al.*, 2008).

This study was designed to evoke first-person kinaesthetic imagery (Jeannerod, 1994). For instance, subjects were shown photographs of walking environments that were taken from a first-person perspective. Furthermore, we exploited the fact that walking along a narrow path requires more voluntary control than walking along a broad path. Accordingly, the path width manipulation directed subjects' attention towards their own movements as they imagined walking along each of the different paths. Subjects were also explicitly instructed to imagine walking along the paths in a first person perspective, and to imagine as if their own legs were moving. Crucially, in a previous related study (Stevens, 2005) it was clearly shown that, under these conditions, subjects' body posture influenced performance of the motor imagery task, but not of the visual imagery task. This provides strong evidence for the presence of first-person kinaesthetic imagery. Therefore, although we don't directly address this issue in this experiment, we believe that the task settings, the explicit instructions, and the previous evidence make it likely that subjects used first-person kinaesthetic imagery during performance of the motor imagery task.

Conclusions

We have provided a replication of the behavioural finding described in Stevens *et al.* (2005), showing that motor imagery of gait is sensitive to the same temporal and spatial constraints as actual walking movements. We have shown that under circumstances that are suitable for a neuroimaging setting it is possible to obtain behavioural indexes that distinguish between motor and visual imagery, and that show the high temporal correspondence between actual and imagined gait. These results open the possibility of using this protocol to explore the neurophysiological correlates of gait control in healthy subjects, and in neurological populations with gait disturbances related to cerebral pathologies, for example, in patients with Parkinson's disease.

Acknowledgements

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Chapter

C4

Cerebral correlates of motor imagery of normal and precision gait

This chapter is based on: Bakker M, de Lange FP, Helmich RC, Scheeringa R, Bloem BR, Toni I (2008). Neuroimage, 1;41(3), 998-1010.

Summary

We have examined the cerebral structures involved in motor imagery of normal and precision gait (i.e., gait requiring precise foot placement and increased postural control). We recorded cerebral activity with functional magnetic resonance imaging while subjects imagined walking along paths of two different widths (broad, narrow) that required either normal gait, or exact foot placement and increased postural control. We used a matched visual imagery task to assess the motor specificity of the effects, and monitored task performance by recording imagery times, eye movements, and electromyography during scanning. In addition, we assessed the effector specificity of motor imagery of gait by comparing our results with those of a previous study on motor imagery of hand movements. We found that imagery times were longer for the narrow path during motor imagery, but not during visual imagery, suggesting that motor imagery was sensitive to the constraints imposed by a narrow walking path. Moreover, motor imagery of precision gait resulted in increased cerebral activity and effective connectivity within a network involving the superior parietal lobules, the dorsal precentral gyri, and the right middle occipital gyrus. Finally, the cerebral responses to motor imagery of gait were contiguous to but spatially distinct from regions involved in motor imagery of hand movements. These results emphasize the role of cortical structures outside primary motor regions in imagining locomotion movements when accurate foot positioning and increased postural control is required.

Introduction

The neural control of locomotion is complex, requiring interactions between locomotor rhythm generation, balance control, and adaptation of the movements to motivational and environmental demands. Studies in cats and rodents have shown that while the production of the basic locomotor rhythm is largely dependent upon activity of central pattern generators within the spinal cord (Dietz, 2003; Grillner and Wallen, 1985), real-life gait also depends upon supra-spinal structures that are involved in adapting walking movements to environmental and motivational demands (Armstrong, 1988). In humans, little is known about the cerebral control of gait. Lesion studies have not been particularly informative, given that cerebral lesions causing higher-level gait disorders are typically multiple, or diffuse (Masdeu, 2001). Transcranial magnetic stimulation has provided electrophysiological evidence that the motor cortex is involved in the control of ankle muscles during walking (Petersen *et al.*, 2001). Similarly, near-infrared spectroscopy has shown specific metabolic responses around the medial aspects of the central sulcus during actual gait (Miyai *et al.*, 2001). In addition, single photon emission computed tomography studies have revealed that cerebral structures outside the primary motor cortex - such as the premotor cortex, parietal cortex, basal ganglia and cerebellum - are also contributing to gait (Fukuyama *et al.*, 1997; Hanakawa *et al.*, 1999b). However, since these studies examined actual gait, they could not distinguish whether those effects were related to the feedforward control of gait or to changes in somatosensory feedback during gait. This issue is an instance of the general distinction that has been drawn between processes leading to the generation of a motor plan (that include predictions of the sensory consequences of the action), and processes related to the evaluation of sensory feedback (Blakemore and Sirigu, 2003; Grush, 2004; Wolpert *et al.*, 1998). In this conceptual framework, it appears relevant to examine the cerebral structures specifically involved in the generation of the motor plan in the absence of sensory feedback due to movement execution. Here we have used motor imagery to address this issue. More specifically, we have examined the cerebral structures involved in motor imagery of both normal and precision gait (i.e., gait requiring precise foot placement and increased postural control).

Motor imagery, i.e. the mental simulation of an action without its actual execution (Jeannerod, 1994; Jeannerod, 2006), has been widely used to study the generation of a movement plan in the absence of sensory feedback (Lotze and Halsband, 2006). This approach relies on the notion that motor imagery involves the generation of a complete motor plan that is prevented from operating on the body (Grush, 2004; Jeannerod, 1994) (for a recent review of empirical support for this notion see Jeannerod, 2006). For instance, it has been shown that the current state of one's own body influences motor imagery performance (de Lange *et al.*, 2006; Parsons, 1994; Shenton *et al.*, 2004; Sirigu and Duhamel, 2001), and that motor imagery, motor preparation, and motor execution share cerebral and physiological correlates (Lang *et al.*, 1994; Deiber *et al.*, 1998; Porro *et al.*, 1996; Roth *et al.*, 1996; Stephan *et al.*, 1995).

A few studies have already examined the cerebral structures involved in motor imagery of gait (Jahn *et al.*, 2004; Malouin *et al.*, 2003; Jahn *et al.*, 2008; Miyai *et al.*, 2001; Sacco *et al.*, 2006), including motor imagery of precision gait (Malouin *et al.*, 2003). More specifically, it was shown that when subjects imagine walking through a series of narrow passages their metabolism increases in the precuneus, the left supplementary motor area (SMA), the right inferior parietal cortex, and the left parahippocampal gyrus compared to when they imagine walking without any obstacles (Malouin *et al.*, 2003). However, it remains unclear which of these cerebral structures is specifically involved in imagining precision gait, rather than spatial navigation, changes in walking direction, or visual imagery processes [see also (Sacco *et al.*, 2006)]. In addition, these and other studies could not provide objective behavioural evidence that the subjects were specifically engaged in motor

imagery of gait during the experiment. More generally, it is important to test whether the brain regions active during imagery of gait are part of a cerebral circuit dedicated to the control of gait, or whether imagery evokes general action plans that are not influenced by the specific effector involved in the action (Glover, 2004; Johnson *et al.*, 2002). Imagery of flexion/extension of toes and fingers recruits separate precentral regions [(Ehrsson *et al.*, 2003), see also (Stippich *et al.*, 2002)], and also imagery of more complex whole body and upper extremity movements reveals a homuncular organization in the primary sensorimotor cortices (Szameitat *et al.*, 2007). However, it remains to be seen whether a similar homuncular somatotopic organization can be found outside the motor strip, and whether it is present for motor imagery of gait.

In this study, we have used a validated motor imagery protocol for examining the cerebral correlates of motor imagery of both normal and precision gait in humans (Bakker *et al.*, 2007a; Stevens, 2005). We asked subjects to imagine walking along visually presented paths of two different widths and five different distances that evoked either normal walking (broad path) or exact foot placement and increased postural control (narrow path). This manipulation allowed us to isolate behavioural and cerebral responses that were influenced by the different environmental constraints associated with imagining walking on supports of different size, distinguishing these responses from the generic effects associated with imagining walking along different distances. Furthermore, we assessed the motoric specificity of the cerebral and behavioural effects by using a matched visual imagery task, in which subjects imagined a disk moving along the same paths and distances used in the motor imagery tasks. Finally, we assessed the effector specificity of motor imagery of gait by comparing it with motor imagery of hand movements (de Lange *et al.*, 2006).

Materials and Methods

Subjects

Sixteen healthy men (age 22±2 years, mean±SD) participated after giving written informed consent according to the Declaration of Helsinki. All subjects had normal or corrected-to-normal vision, and no neurological or orthopaedic disturbances. All participants were consistent right-handers (Edinburgh Handedness Inventory (Oldfield, 1971) score 84±12 %, mean±SD). The study was approved by the local ethics committee.

Experimental set-up

During the experiment, subjects were lying supine in the MR scanner. Head movements were minimized by an adjustable padded head holder. Visual stimuli were projected onto a screen at the back of the scanner and were seen through a mirror above the subjects' heads. The stimuli subtended a visual angle of ~10°. Stimuli presentation was controlled through a PC running Presentation software (Neurobehavioural systems, Albany, USA). Button presses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI), positioned on the right side of the subject's abdomen.

Stimuli

We used 20 photographs, each showing the same corridor with a path in the middle (path length = 12 m; thickness = 3 mm). There were narrow and broad paths (PATH WIDTH: 9 and 27 cm - see Fig. 4.1). The broad path allowed for walking over the path with a normal gait, whereas the narrow path required the subjects to carefully position their feet one in front of the other. At the near-end of the linoleum path there was either a green square (64 cm2) or a black disc (diameter: 7.5 cm, width: 2.5 cm).

Along the linoleum path there was a green pillar (diameter: 7.5 cm, width: 12 cm), placed at one of five different distances from the green square or the black disc (PATH LENGTH: 2, 4, 6, 8 and 10 m). This resulted in a total of 20 photographs (2 start markers x 5 path lengths x 2 path widths).

Tasks

Subjects performed two tasks: motor imagery (MI) and visual imagery (VI). Both tasks started with the presentation of one of the photographs described above, with the green square during MI trials, and the black disk during VI trials (Fig 4.1). During MI, subjects were asked to imagine walking along the path shown in the photograph, starting from the green square and stopping at the green pillar. During VI, subjects were asked to imagine seeing the black disc moving along the path, from its starting position until the green pillar.

During each trial, after a short inspection of the photograph on display, the subjects closed their eyes and imagined standing on the left side of the path, next to the green square (MI trials – for trial time course see Fig 4.2) or the black disk (VI trials). The subjects pressed a button with the index finger of their right hand to signal that they had started imagining to step onto the path and walking along the path (MI trials), or imagining to see the disc moving along the path (VI trials). Subjects pressed the button again when they imagined that they had reached the end of the walking trajectory (MI trials), or that the disc had reached the end of the walking trajectory (VI trials). Following the second button press, a fixation cross was presented on the screen (inter-trial interval, ITI: 4-12 sec), and the subjects could open their eyes. A transient change in size of the fixation cross announced the start of the next trial, i.e. the presentation of a new photograph of the corridor.

Experimental procedures

The MI and VI tasks were performed in two experimental sessions of 30 min each, separated by a break outside the scanner. Task order was counter-balanced across subjects. We have chosen a clustered task presentation to avoid the task-switching effects likely evoked by a trial-by-trial or block-by-block alternation between the two imagery tasks. We were concerned that task-switching might become especially problematic when the same experimental set-up would be used in follow-up studies on patient populations. An additional problem of a mixed task presentation is that the task instructions should be given at once for both tasks. This might make the task too complicated for some patient groups. For each session, the trial order was pseudo-randomized across the experimental factors [i.e., PATH WIDTH (2 levels) and PATH LENGTH (5 levels)].

Before we started the experiment, subjects were familiarized with the actual paths and corridor, as shown in the photographs. The subjects were informed that, during the experiment, they would be shown photographs of these paths. They were then given written instructions for the first experimental session, followed by training in the relevant task, first outside the scanner (15 trials), and then inside the MR-scanner (7 trials). During the break between the first and second experimental session, the subjects were given written instructions for the second session, followed by training outside the MR-scanner until subjects felt confident they could perform the task (maximally 15 trials).

Prior to the MI task, subjects were asked to walk along short versions (three meters) of both the broad and the narrow linoleum paths (3 times for each path width), at a comfortable pace, avoiding to place their feet outside the path. We instructed subjects to pay attention to the feeling of walking along the different path widths, and to imagine walking in a similar way along the two different paths during the imagery trials. We instructed subjects to imagine the walking movement as vividly

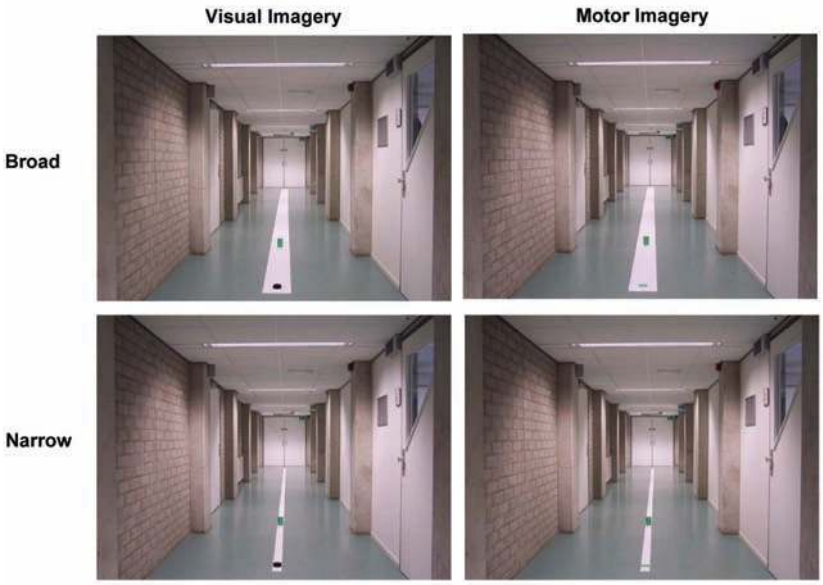


Figure 4.1 Stimuli. *Examples of photographs of walking trajectories presented to the subjects during the motor imagery (MI), and visual imagery (VI) experiment. The photographs show a corridor with a white path in the middle and a green pillar positioned on the path. During MI trials, a green square is present at the beginning of the path. During VI trials, a black disc is present at the beginning of the path. During both tasks, the path width can be either broad (27 cm), or narrow (9 cm). In addition, the green pillar can be positioned at 2, 4, 6, 8 or 10 m from the green square or black disc (2 m in the photos presented in this figure).*

as possible, in a first person perspective, as if their legs were moving, but without making any actual movements. Prior to the VI task, subjects were familiarized with the actual black disc shown in the photographs, and they saw a video of the disc moving through the same corridor as in the photographs, but without a linoleum path in the middle of the corridor. The disc moved for 6 m, in a straight line, at a uniform speed of about 0.8 m/s. We instructed subjects to imagine seeing the disc moving in a similar way along the two different paths during the imagery trials. We instructed subjects to imagine seeing the disc moving as vividly as possible, without making any actual movements.

We recorded muscle activity of the legs during both sessions to control for overt muscle movements. To assess the reliability of this measure, we asked subjects (after the second session) to perform dorsiflexion movements of their right foot during MR acquisition at four different levels of contraction: no contraction (0%); minimal contraction (1%); half- maximal contraction (50%); maximal contraction (100%). Each contraction was triggered by the corresponding label (0%, 1%, 50%, 100%), and the subjects were asked to contract their muscle for as long as the label was presented on the screen. Each contraction lasted 10 sec, followed by 30 sec rest, and it was repeated two times in a semi-random order.

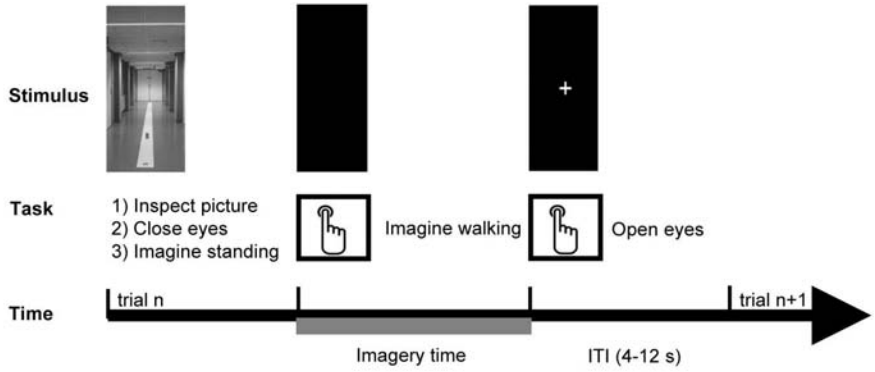


Figure 4.2 Time course of motor imagery trials. *During each trial, after a short inspection of the photo on display, the subjects closed their eyes and imagined standing on the left side of the path, next to the green square. The subjects were asked to press a button with the index finger of their left or right hand to signal that they had started imagining to step onto the path and walking along the path. The subjects were also asked to press the button again when they imagined having reached the end of the walking trajectory. Following the second button press, a fixation cross was presented on the screen and the subjects could open their eyes. The duration of the inter-trial interval (ITI) was 4-12 s.*

Data collection

MR images were acquired on a 3 Tesla Trio MRI system (Siemens, Erlangen, Germany), using a standard circular polarized head coil for radio-frequency transmission and signal reception. Blood oxygenation level-dependent (BOLD) sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE = 2360 ms/30 ms; 50 ms gap between successive volumes; 36 transversal slices; ascending acquisition; voxel size 3.5 x 3.5 x 3.5 mm^3; FOV = 224 mm^2). High-resolution anatomical images were acquired using an MP-RAGE sequence (TE/TR 3.93/2300 ms, 192 sagittal slices, voxel size 1.0 x 1.0 x 1.0 mm^3, FOV 256 mm^2).

Muscle activity (EMG) was measured during task performance in the MR-scanner (MI, VI, and voluntary foot contractions) with a pair of carbon wired MRI compatible sintered silver/silver-chloride electrodes (Easycap, Herrsching-Breitbrunn, Germany), placed 3 cm apart along the muscle bellies of the right tibialis anterior. A neutral electrode was placed on the centre of the patella. Following amplification and A/D conversion (Brain Products GmBH, Gilching, Germany), an optical cable fed the EMG signal to a dedicated PC outside the MR room for further off-line analysis (sampling rate: 5000 Hz). MR artefact correction followed the method described by (Allen *et al.*, 2000; van Duinen *et al.*, 2005), including low-pass filtering (400 Hz), and down-sampling (1000 Hz). Finally, we applied high-pass filtering (10 Hz, to remove possible movement artefacts), and rectification.

Eye movements were measured during task performance in the MR-scanner with a video-based infrared eyetracker (Sensomotoric Instruments, Berlin, Germany). Movements of the left eye were sampled at 50 Hz and fed to a dedicated PC outside the MR room for further off-line analysis.

Behavioural analysis and statistical inference
For each trial, we measured the time between the two button presses that marked the start and the end of the imagined visual or walking movements [imagery time, see Fig. 4.2]. We excluded those few trials in which the subjects pressed the button only once, and therefore opened their eyes before the end of the imagery time, as revealed by online inspection of the eyetracker data. For clarity, experimental factors are marked in upper case (i.e., TASK), levels within a factor are marked in small caps (i.e., MI). We investigated the effect of TASK (MI, VI), PATH WIDTH (NARROW, BROAD), and PATH LENGTH (2, 4, 6, 8, 10 m) on imagery time. The significance of the experimental factors was tested using a $2 \times 2 \times 5 \times 2$ repeated measures ANOVA. When interactions were significant, the simple main effects were investigated by additional repeated measures ANOVAs. The alpha-level of all behavioural analyses was set at $p < 0.05$. Greenhouse-Geisser corrections were applied whenever the assumption of sphericity was not met, resulting in adjusted P-values based on adjusted degrees of freedom. In addition, we examined whether imagery time obtained in each task conformed to Fitts' law (Fitts, 1954):

$$\text{Movement time} = a + b \log_2(2^* \text{ PATH LENGTH} / \text{PATH WIDTH})$$

In the equation, a and b are constants. The term $\log_2(2^*$ PATH LENGTH / PATH WIDTH) is called the index of difficulty (ID). It describes the difficulty of the motor tasks. We calculated ID for each of our 10 experimental conditions [i.e., PATH WIDTH (2 levels) and PATH LENGTH (5 levels)]. The imagery time of conditions with the same ID value were averaged. Fitts' Law states that imagery time increases linearly with increasing ID. We examined how well imagery time conformed to Fitts' Law by calculating the linear regression of imagery time over ID for each task and for each subject separately. Finally, we examined whether the degree to which imagery time conformed to Fitts' Law was different for the different tasks, by considering the effect of TASK (MI, VI) on the variance in imagery time that could be explained by ID (r^2) after fisher's z-score transformation using a paired sample t-test.

EMG analysis and statistical inference
For each trial of the imagery experiment, we considered the root mean square (rms) of the EMG signals measured during the imagery time (imagery epoch) and during the ITI (intertrial epoch - Fig 4.2). For each subject, the average rms value of the EMG measured during the imagery epoch was normalized to the average rms value of the ITI epoch, testing for an effect of TASK (MI, VI) with a paired samples t-test.

For the voluntary foot movement task, we considered the root mean square (rms) of the EMG signals measured during the 10 sec contraction (contraction epoch) and during the 20 sec preceding the contraction (intertrial epoch). For each subject and for each of the four level of contraction (0%, 1%, 50%, 100%), the average rms value of the EMG measured during the contraction epoch was normalized to the average rms value of the intertrial epoch, testing for an effect of CONTRACTION (0%, 1%, 50%, 100%) with a repeated measures ANOVA and post-hoc paired sample t-tests.

fMRI analysis - preprocessing

Functional data were pre-processed and analyzed with SPM2 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first four volumes of each participant's data set were discarded to allow for T1 equilibration. Afterwards, the image time series were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations, rotations) by minimizing head-movements between each image and the reference image (Friston *et al.*, 1995b). Subsequently, the time-series for each voxel was temporally realigned to the acquisition of the first slice. Images were normalized to a standard EPI template centred in MNI (Montreal Neurological Institute) space (Ashburner and Friston, 1997) by using linear transformations and resampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 10 mm full-width-at-half-maximum Gaussian kernel. Anatomical images were spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images.

fMRI analysis – Statistical inference (first level)

The ensuing pre-processed fMRI time series were analyzed on a subject-by-subject basis using an event-related approach in the context of the General Linear Model (Friston *et al.*, 1995a). For each subject, regressors of interest were defined to characterize the cerebral response to imagery performed in each of the twenty different conditions of the 2 x 2 x 5 design [i.e., TASK (MI, VI), PATH WIDTH (NARROW, BROAD) and PATH LENGTH (2, 4, 6, 8, 10 m)]. Other regressors of no interest modelled the cerebral response to picture inspection, button presses, and incorrect trials (i.e. those few trials in which the subjects pressed the button only once, and therefore opened their eyes before the end of the imagery time, as revealed by online inspection of the eyetracker data). Each effect was modelled on a trial-by-trial basis as a concatenation of square-wave functions convolved with a canonical haemodynamic response function, down-sampled at each scan, generating a total of 26 task-related regressors (Friston *et al.*, 1998). For the regressors of interest, onsets of the square-wave functions were time-locked to the button press marking the onset of imagery, and durations corresponded to the mean imagery time across all imagery trials of the subject. For the picture inspection regressors, onsets were time locked to the onset of picture presentation, and offsets were time-locked to the button press marking the onset of imagery. For the button press regressor, onsets were time locked to the button press marking the offset of imagery, and duration was set at zero. For the incorrect trial regressor, onsets were time locked to the onset of picture presentation, and offsets were time-locked to the button press marking the offset of imagery. We also included 6 head motion regressors (describing translation and rotation in each of the three dimensions) and their temporal derivative, as derived from the spatial realignment procedure in the statistical model. Data were high-pass filtered (cutoff, 128 s) to remove low-frequency confounds such as scanner drifts. The statistical significance of the estimated evoked haemodynamic responses was assessed using t-statistics in the context of the General Linear Model. For each subject, we calculated contrasts of the parameter estimates for the effects of TASK and PATH WIDTH (i.e. MI-BROAD, MI-NARROW, VI-BROAD, VI-NARROW). We also considered linear parametric modulations of PATH LENGTH for each of these four effects (i.e. MI-BROAD-DISTANCE, MI-NARROW-DISTANCE, VI-BROAD-DISTANCE, VI-NARROW-DISTANCE), generating a total of eight contrasts for each subject.

fMRI analysis – Statistical inference (second level)

The group-level random effects analysis modelled the experimental variance described by the eight contrasts for each subject by means of a one-way between-subjects analysis of variance (ANOVA), with non-sphericity correction. First, we considered the main effect of TASK (MI, VI). This refers to differential cerebral activity between the two tasks (MI > VI; VI > MI). Second, we looked for

MI-specific effects of environmental constraints. This refers to differential cerebral activity evoked during MI between the two path widths (MI-broad > MI-narrow; MI-narrow > MI-broad). We were specifically interested in those regions that were specifically involved in MI, and increased their activity as a function of path width during MI, but not during VI. One way to fulfil these constrains while maintaining sensitivity is to mask the simple main effect (for instance, MI-narrow > MI-broad) with the main effect of task [i.e. MI>VI] and the relative interaction [i.e. (MI-narrow > MI-broad) > (VI-narrow > VI-broad); see also (Ramnani *et al.*, 2001)]. In other words, when testing for the differential cerebral activity evoked during MI between the two path widths, we confined our search to regions showing a main effect of TASK (MI > VI) and a corresponding TASK X PATH WIDTH interaction [(MI-broad > MI-narrow) > (VI-broad > VI-narrow); (MI-narrow > MI-broad) > (VI-narrow > VI-broad)], using inclusive masking. An equivalent procedure was used to assess the effects of PATH WIDTH during VI. Third, we looked for MI-specific effects of imagined walking distance. This refers to cerebral activity that increased linearly as a function of PATH LENGTH during MI performance (MI-dist). We were again specifically interested in those regions that were involved in MI, and increased their activity as a function of path length during MI, but not during VI. Therefore, when testing for cerebral activity that increased linearly as a function of PATH LENGTH during MI performance, we confined our search to regions showing a main effect of TASK (MI > VI) and a corresponding TASK X PATH LENGTH interaction [(MI-dist > VI-dist)], using inclusive masking. An equivalent procedure was used to assess the effects of DISTANCE during VI. A list of the contrasts and functional masks used in this study is presented in Table 4.1. SPMs of the T statistic for these effects were created. We report the results of a random effects analysis, with inferences drawn at the voxel level, corrected for multiple comparisons across the whole brain using family-wise error (FWE) correction ($p<0.05$).

Table 4.1 Contrasts tested in the Random Effects Analysis.

Experimental factor	Contrasts	Functional (inclusive) Masks
Task	MI > VI	
	VI > MI	
Path width	MI narrow > MI broad	a) MI > VI b) (MI narrow > MI broad) > (VI narrow > VI broad)
	MI broad > MI narrow	a) MI > VI b) (MI broad > MI narrow) > (VI broad > VI narrow)
	VI narrow > VI broad	a) VI > MI b) (VI narrow > VI broad) > (MI narrow > MI broad)
	VI broad > VI narrow	a) VI > MI b) (VI broad > VI narrow) > (MI broad > MI narrow)
Path length	MI distance	a) MI > VI b) MI distance > VI distance
	VI distance	a) VI > MI b) VI distance > MI distance

MI = motor imagery; VI = visual imagery

Effective connectivity analysis

After having identified regions in the left and right superior parietal lobule (SPL) and the right middle occipital gyrus (MOG) that were specifically involved in motor imagery of gait along a narrow path, we performed a post-hoc analysis to explore which brain areas increased their couplings with these three regions during motor imagery of precision gait. To address this issue, we used the psychophysiological interaction (PPI) method described by (Friston *et al.*, 1997). PPI analysis makes inferences about regionally specific responses caused by the interaction between the psychological factor and the physiological activity in a specified index area. We tested for differences in the regression slope of cerebral activity (on a voxel-by-voxel basis) on the basis of the activity in three source regions (e.g. left & right SPL, and right MOG, Fig. 4.5, Table 4.3), depending on the width of the path (broad or narrow) and the epoch of the motor imagery trial (picture presentation versus imagery). More specifically, the psychological factor was a vector coding for the interaction between the effect of path width during the motor imagery epoch, and the picture presentation epoch [i.e., (MI narrow > MI broad) > (Picture presentation narrow path > Picture presentation broad path)]. The source regions were defined by the first eigenvariate of the time series of all voxels within a 6 mm radius sphere centred on the regional maxima in the three source regions that showed a relative increase in BOLD signal during motor imagery of gait along a narrow compared to a broad path (MI-narrow > MI-broad; $p<0.5$ uncorrected). First, a PPI analysis for each subject and each source region was performed at the first level. Then, for each source region, individual PPI contrast images were entered into one-sample t-test at the second level. The statistical inference ($p < 0.05$) was performed at the voxel-level, using FWE correction for multiple comparisons over a search volume defined by those voxels that were activated in the contrast MI>VI (as defined above).

fMRI analysis – Anatomical inference

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of the subjects. The atlas of (Duvernoy *et al.*, 1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann Areas were assigned on the basis of the SPM Anatomy Toolbox (Eickhoff *et al.*, 2005), i.e., the anatomical position of our significant clusters and local maxima was formally tested against published three-dimensional probabilistic cytoarchitectonic maps. Finally, we compared our results with a previous study on motor imagery of hand movements (de Lange *et al.*, 2006), to assess the relative anatomical location of the activated brain regions observed during MI of gait and during MI of hand rotations. More specifically, we compared the anatomical locations of our cerebral activity to that of cerebral areas showing increased cerebral activity with increasing biomechanical complexity during either left or right hand rotations, after using FWE correction to correct for multiple comparisons across the whole brain. Given that the whole brain analysis on MI of hand rotations did not reveal any suprathreshold cerebral activity in the putamen (whereas our whole brain analysis on MI of gait did), we also performed a dedicated VOI analysis in the putamen during MI of hand rotations using the Pick Atlas (Maldjian *et al.*, 2003; Maldjian *et al.*, 2004).

Results

Behavioural performance

There were no significant differences in imagery times between the two tasks (main effect of TASK: $F(1,14) = 2.9$, $p = 0.1$). In both tasks, imagery time increased with increasing path length (main effect of PATH LENGTH: $F(1.1,15.6) = 155.3$, $p< 0.001$ - Fig. 4.3A,B). Crucially, the effect of path width on imagery time differed for the different tasks (TASK x PATH WIDTH interaction: $F(1,14) = 39.5$, $p<0.001$). A smaller path width resulted in longer imagery time in the MI task

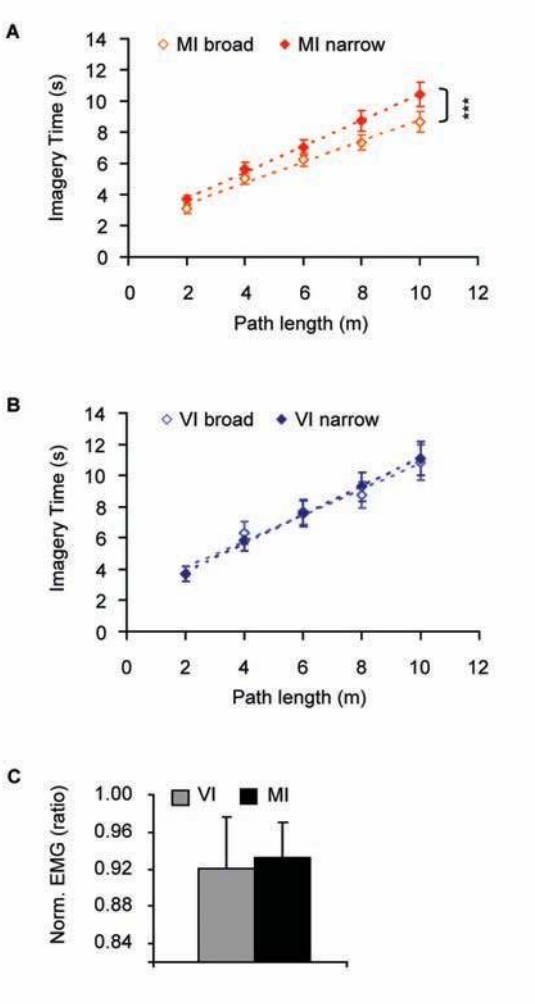


Figure 4.3 Behavioural performance. *Imagery times are shown for each of the five different path lengths (2, 4, 6, 8, and 10 m), and the two different path widths [Broad (27 cm), and Narrow (9 cm)], separately for each of the two tasks [**A)** motor imagery (MI), and **B)** visual imagery (VI)]. **C)** Averaged normalized electromyography (Norm. EMG) values measured during MI and VI trials, normalized to average intertrial interval EMG values on a subject by subject basis (imagery EMG / intertrial interval EMG). Data represent mean ± SEM. ***P < 0.001.*

($F(1,14) = 37.0$, $p<0.001$) (Fig. 4.3A), but had no effect on imagery time in the VI task ($F(1,14) = 0.3$ $p=0.6$) (Fig. 4.3B). Finally, imagery time correlated linearly with ID in both tasks. Crucially, the variance in imagery time that could be explained by ID (r^2) was greater for MI (0.69 ± 0.03) than for VI (0.50 ± 0.01) (main effect of TASK: $F(1,15) = 32.8$, $p<0.001$).

Muscular activity

We found no significant differences in EMG activity between the two tasks (main effect of TASK: ($F(1,15) = 0.1$, $p = 0.7$ - Fig. 4.3C). This result was unlikely to be due to lack of sensitivity, as we could find (in the same experimental setting) a significant effect of the amount of muscle contraction on EMG activity during voluntary contractions (main effect of CONTRACTION: $F(3,45) = 45.4$, $p<0.001$), with significant differences between each of the four different levels of contraction (no contraction versus minimal contraction: $p<0.01$; minimal versus half-maximal contraction: $p<0.05$; half-maximal versus maximal contraction: $p<0.001$).

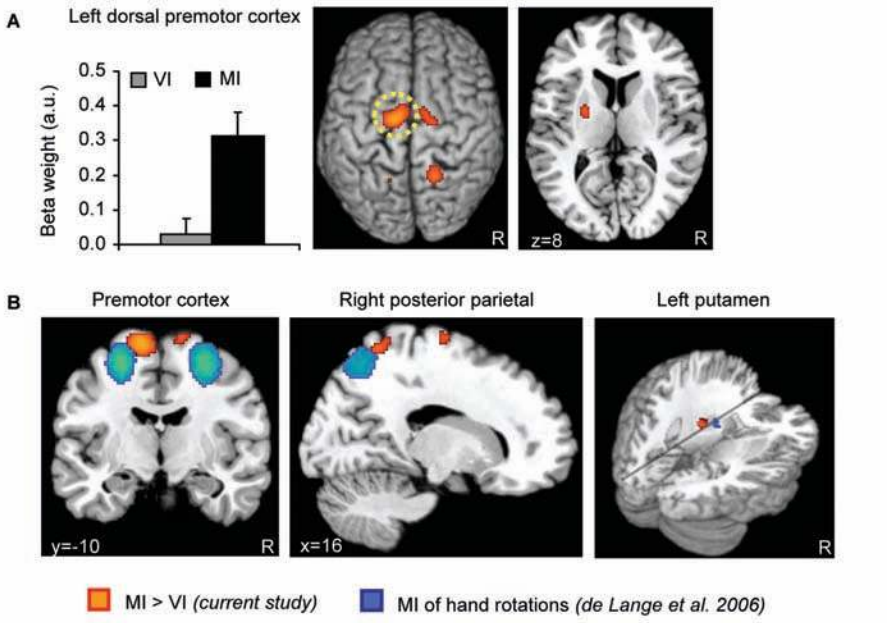


Figure 4.4 Cerebral activity during motor imagery of gait. A) *On the left, beta weights (mean ± sem) of the local maximum from left dorsal premotor cortex, separately for motor imagery (MI) and visual imagery (VI). On the right, statistical parametric map (SPM) of increased activity in the left putamen, in the right superior parietal lobule, and bilaterally in the dorsal premotor cortex during MI compared to VI [corrected for multiple comparisons ($p<0.05$) using family wise error (FWE)], superimposed on a rendered brain viewed from the top (middle panel), and on a transverse brain section (right panel).* ***B)*** *SPMs ($p<0.05$ FWE-corrected for multiple comparisons) of increased cerebral activity during MI of gait (compared to VI, in red-orange), and during MI of hand rotations (i.e. linear increase in activity with increasing stimulus rotation, in blue-cyan). R = right.*

Cerebral activity – TASK effects

We first identified cerebral regions showing differential activation during MI compared to VI (Fig. 4.4, Table 4.2). Cerebral activity was greater during MI than VI in two clusters extending from the dorsal precentral sulcus to the superior frontal gyrus, bilaterally. Both clusters fell within BA6 (100%), but given the lack of cyto-architectonic studies on the border between lateral premotor cortex and supplementary motor area (SMA) proper in humans, it is difficult to draw precise inferences on the functional label of these superior frontal activations. A recent meta-analysis of functional imaging studies (Mayka *et al.*, 2006) remains inconclusive, placing these activations at the border between the lateral premotor cortex and the SMA-proper. However, in macaques, as one moves from dorsal premotor cortex to SMA along a lateral-to-medial direction, the leg representation in dorsal premotor cortex is followed by the hand/arm representation in SMA, and then, more ventrally, by the leg representation in SMA (Luppino and Rizzolatti, 2000; Mitz and Wise, 1987). Crucially, the hand/arm representation in SMA partially extends on the lateral convexity, whereas the leg representation in SMA is located in the bank of the inter-hemispheric fissure. Under the

assumption that our superior frontal activations are likely related to motor planning of the leg, and given that these activations are located exclusively in the dorsal convexity, we tentatively label them as dorsal premotor cortex caudal (PMdc) (Picard and Strick, 2001). The cingulate gyrus also showed increased neural activity during MI compared to VI. This cluster fell within the right BA6 (100%) (Eickhoff *et al.*, 2005), and its local maximum can be functionally labelled as right rostral cingulate zone posterior (RCZp) (Picard and Strick, 1996). Furthermore, significant activation was found in the right SPL, and there was a marginally significant activation in the left SPL (p=0.051). Both parietal clusters fall caudal to BA2 (3% for right part, 0% for left part) (Eickhoff *et al.*, 2005). Finally, significant activity was found in the left putamen. We also found a trend of increased cerebral activity in the right cerebellum ([36 -52 -34]; T=4.46, p=0.079, FWE).

Table 4.2 Stereotactic coordinates of the local maxima activated in the contrast "MI > VI". Results are corrected for multiple comparisons across the whole brain (FWE, p<0.05). Stereotactic coordinates are reported in MNI (Montreal Neurological Institute) space. Details on the anatomical and functional labelling can be found in the Methods and Results sections.

Contrast	Anatomical label	Functional label	Hemi-sphere	T-value	P-value	x	y	z
MI > VI	Superior frontal gyrus	Dorsal premotor caudal	L	6.21	<0.001	-12	-10	68
	Superior frontal gyrus	Dorsal premotor caudal	R	5.00	0.013	16	-12	74
	Anterior cingulate gyrus	Rostral Cingulate Zone Post	R	4.64	0.045	6	0	46
	Superior parietal lobule		R	5.50	0.002	20	-56	68
	Superior parietal lobule		L	4.60	0.051	-16	-58	60
	Putamen		L	5.01	0.012	-24	-4	8

L = left; MI = motor imagery; Post = Posterior; R = right; VI = visual imagery;

In order to address the issue of a possible somatotopic organization of the MI-related activity found in the present study, we compared our results with those of a previous study on motor imagery of hand rotations (de Lange *et al.*, 2006). The local maxima of both our left and right frontal clusters were located medially (12 and 14 mm, respectively) and dorsally (14 and 18 mm, respectively) from the local maxima of the corresponding frontal clusters activated during motor imagery of hand movements (Fig. 4.4B). There were no substantial differences in the rostro-caudal direction (2 mm). The local maxima of both our left and right parietal clusters were located rostrally (8 and 10 mm, respectively) and dorsally (12 and 16 mm, respectively) from the local maxima of the parietal clusters activated during motor imagery of hand movements (Fig. 4.4B). There were no substantial differences in the medio-lateral direction (2 and 0 mm, respectively). The local maximum of our

left putamen activity was located laterally (6 mm), caudally (16 mm), and dorsally (10 mm) from the local maxima of the left putamen cluster activated during motor imagery of hand movements (Fig. 4.4B).

There were no areas that were more strongly activated during VI than during MI, i.e. VI was contained within MI.

Table 4.3 Stereotactic coordinates of the local maxima activated in the contrast "MInarrow > MIbroad". Results are corrected for multiple comparisons across the whole brain (FWE, p<0.05). Stereotactic coordinates are reported in MNI (Montreal Neurological Institute) space. Details on the anatomical labelling can be found in the Methods and Results sections.

Contrast	Functional (inclusive) masks	Anatomical label	Hemi-sphere	T-value	P-value	x	y	z
MInar>MIbr	"MI>VI" & "(MInar>MIbr) > (VInar>VIbr)"	Superior parietal lobule	L	4.97	0.014	-16	-50	64
		Superior parietal lobule	R	4.88	0.019	16	-54	64
		Superior middle occipital gyrus	R	5.05	0.011	56	-70	12

br = broad; L = left; MI = motor imagery; nar = narrow; R = right; VI = visual imagery

Cerebral activity – PATH WIDTH effects

We identified regions showing a differential effect of path width during MI compared to VI. We found increased activity in the left and right SPL during MI along a narrow compared to a broad path (Fig. 4.5A, Table 4.3). Both clusters fell caudal to the probability range of BA2 (left: 9.2%, right: 0%) (Eickhoff *et al.*, 2005), and it can be seen that in both regions cerebral activity increases with smaller path width during MI, but that cerebral activity is not influenced by path width during VI. We also found increased cerebral activity in the superior middle occipital gyrus (sMOG). The peak of this cluster was outside area V5/MT+ (probability range: [0-10%]) (Eickhoff *et al.*, 2005). When comparing the anatomical localization of sMOG to previous studies describing activity in the extrastriate body area (EBA), its respective displacement was 12 mm (Downing *et al.*, 2001), 10 mm (Saxe *et al.*, 2006) and 17 mm (Astafiev *et al.*, 2004). Although there was no significant activation in the PMd or cerebellum at corrected threshold, trends were visible in both these areas at uncorrected threshold (left PMd [-26 -8 66]; T=3.68, p<0.001, uncorrected; left cerebellum [-40 -40 -32]; T=3.42, p<0.001, uncorrected).

We found no cerebral regions that decreased their activity with smaller path width during MI. There were also no cerebral regions that showed larger modulation by path width during the VI task than during MI. Finally, we found no regions that showed a task x path width interaction.

Cerebral activity – PATH LENGTH

Finally, we identified regions showing a differential effect of path length during MI compared to VI. We found that the superior frontal gyrus and right cerebellum increased their activity with increasing path length during MI (Table 4.4). The cluster in the superior frontal gyrus fell within the probability range (100%) of BA6 (Eickhoff *et al.*, 2005), and its local maximum can be function

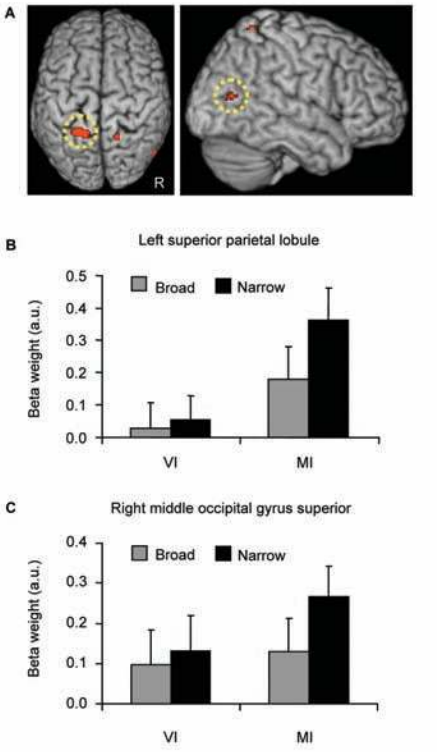


Figure 4.5 Effect of path width on cerebral activity during motor imagery of gait. A) *Statistical parametric map (p<0.05 FWE-corrected for multiple comparisons) showing increased cerebral activity in the left and right superior parietal lobule and in the right middle occipital gyrus during motor imagery (MI) along a narrow path (compared to MI along a broad path), superimposed on a rendered brain viewed from the top (left panel) and from the right (right panel). This simple main effect was searched within those voxels showing a Task X Path Width interaction, i.e. stronger effects of path width during the MI task than during the VI task.* ***B,C)*** *Beta weights (mean ± sem) of the local maxima of the left superior parietal lobule and the right middle occipital gyrus for each of the two different path widths (broad, narrow), separately for MI and VI, and for the five different distances. R = right.*

ally labelled as SMA (Picard and Strick, 1996). The effect sizes show that cerebral activity increases with increasing path length during both MI and VI, but that the effect is greater for MI than for VI. We found no cerebral regions that showed larger modulation by path length during the VI task than during MI. Finally, we found no regions that showed a task x path length interaction.

Table 4.4 Stereotactic coordinates of the local maxima activated in the contrast "MI distance". Results are corrected for multiple comparisons across the whole brain (FWE, p<0.05). Stereotactic coordinates are reported in MNI (Montreal Neurological Institute) space. Details on the anatomical and functional labelling can be found in the Methods and Results sections.

Contrast	Functional (inclusive) masks	Anatomical label	Functional label	Hemisphere	T-value	P-value	x	y	z
MI dist	"MI>VI" "MIdist > VIdist"	Superior frontal gyrus, medial part	SMA	L	6.21	<0.001	-6	-4	64
		Cerebellum (lobule VI)		R	5.55	0.002	40	-52	-26

dist = distance; L = left; MI = motor imagery; R = right; SMA = supplementary motor area; VI = visual imagery

Cerebral activity - Effective connectivity

From the contrasts mentioned above, it appeared that the left and right SPLs and the right sMOG were specifically involved in motor imagery of gait along a narrow path (as compared to a broad path). We tested whether these regions contributed to motor imagery by examining whether its activity influenced the network supporting the motor imagery process (Fig 4.4A). We found that the right sMOG increased its coupling as a function of path width with the right PMd ([16, -10, 72]; T=4.52; P=0.012, FWE corrected), and supplementary motor area ([-6, 0, 70]; T=4.74; P=0.008, FWE corrected). The right SPL increased its coupling as a function of path width with the left PMd ([-10, -4, 77]; T=5.86; P=0.001, FWE corrected).

Discussion

In this study we examined the cerebral structures involved in motor imagery of normal and precision gait. We distinguished imagery-related effects influenced by environmental constraints from generic imagery-related effects, and controlled for changes in muscle activity. We found that the activity and the inter-regional couplings between bilateral SPL, the dorsal precentral gyri, and the right sMOG were modulated by the degree of spatial accuracy of the imagined gait movements, with activity and connectivity increasing when subjects imagined walking along a narrow path requiring accurate positioning of each foot. These effects were specific to the MI task, resulting from a direct comparison with a matched visual imagery task. These effects were not related to differences in duration or number of steps between the two tasks, i.e. changes in path length did not influence cerebral activity in these regions during motor imagery of gait. These effects were embedded within a set of cerebral structures (PMd, RCZp, putamen, and cerebellum) with increased activity during motor imagery of gait, again compared to a matched visual imagery task. Furthermore, the parietal, premotor and putamen effects were contiguous but spatially distinct from activity evoked during motor imagery of hand movements (de Lange *et al.*, 2006). These results indicate that in humans the precise spatial control of imagined gait relies on functional interactions between the SPL, the precentral gyrus, and the superior middle occipital gyrus. In the following sections, we discuss these findings and their relevance for current models of gait control.

Behavioural performance

The procedures used in this study were designed to isolate specific effects of first person kinesthetic motor imagery of gait, while excluding the presence of actual leg movements. We recorded EMG during task performance, showing that muscular activity during both MI and VI was matched (Fig. 4.3C). We recorded imagery times on a trial by trial basis, showing that imagery time increased as a function of path width during the MI trials, but not during the VI trials. This result indicates that motor imagery was sensitive to the environmental constraints imposed by a narrow walking path that allows only for positioning one foot at a time on the path. Furthermore, during motor imagery, there was an inverse and logarithmic relationship between movement difficulty and imagined movement time (Fitts, 1954). Visual imagery trials did not follow this rule of human movements. Finally, this task was adapted from a previous study showing that performance of motor imagery, but not visual imagery, was influenced by subjects' body posture (Stevens, 2005). Taken together, these findings provide evidence that the subjects solved the task by using first person kinaesthetic imagery, without making any actual movement.

A distributed and dedicated circuit for motor imagery of gait

Motor imagery of gait resulted in increased cerebral activity bilaterally in the PMd, in the SPL, in the right RCZp, and in the left putamen. In addition, cerebral activity tended to be increased in the right cerebellum. These increases were relative to a matched visual imagery task, designed to control for unspecific effects (such as pressing a button, or general imagery-related effects). It

should be noted that some of the cerebral effects we report might be related to imagined changes in the surrounding visual environment, given that during the visual imagery task subjects were instructed to see the black disc moving, while their own position remained fixed. These changes are likely to be part of the expected sensory consequences of the imagined movements, as will be discussed later. Furthermore, it might be argued that this comparison did not adequately control for accessory strategies, like counting, but it is unlikely that counting could account for the present results. Enumerating sequential foot movements modulates cerebral activity in the lateral premotor cortex (Kansaku *et al.*, 2006), i.e. in locations that were considerably (> 36 mm) lateral and ventral from the present effects.

It is possible that motor imagery relies on general action plans that are not effector-specific (Glover, 2004; Johnson *et al.*, 2002), but our results suggest otherwise. We found that the cerebral responses to motor imagery of gait were contiguous to but spatially distinct from regions involved in motor imagery of hand movements. The somatotopic pattern described in this study fits with the findings of single-unit recordings in macaques, showing that in the premotor cortex the foot is represented in a location more medial and caudal than that of the hand (Godschalk *et al.*, 1995; He *et al.*, 1993; Kurata, 1989), whereas in the posterior parietal cortex the lower limb is rostral to the upper limb (Murray and Coulter, 1981). It remains to be seen how these findings can be reconciled with the opposite somatotopy found in single-subjects PET analyses of human parietal area 5 during actual arm and leg movements (Fink *et al.*, 1997). Finally, in the putamen, cerebral activity during MI of gait was lateral, caudal, and dorsal to activity during MI of hand rotations. The dorsal and lateral location of foot relative to hand representations is in agreement with previous studies in humans (Gerardin *et al.*, 2003; Lehericy *et al.*, 1998; Maillard *et al.*, 2000; Scholz *et al.*, 2000), although the more caudal location of foot relative to hand is opposite to what has been reported before (Lehericy *et al.*, 1998). Taken together, these findings suggest that motor imagery of gait activated cerebral structures that were specific for the effector used, although it remains to be seen whether the relative displacements of the results are consistent within subjects. It might be argued that the differences in spatial activation patterns between the MI of gait and MI of hand rotation may be attributable to differences in the reference frame of the movements. However, while it is generally accepted that different effectors are controlled by spatially separate portions of the primate precentral cortex (Graziano and Aflalo, 2007), it is less clear whether neurons encoding movements in different reference frames have such a clear spatial separation (Pesaran *et al.*, 2006).

Over the precentral gyrus, activities evoked during MI of gait and during execution of right foot movement were spatially segregated (see supplementary Fig. 4.1), a further indication that primary motor cortex is not specifically involved in motor imagery (de Lange *et al.*, 2005).

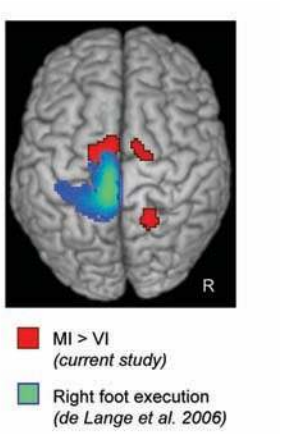
We did not find any activity in brainstem structures during motor imagery of gait. Our study therefore does not confirm the finding by Jahn *et al.* (2008) that motor imagery of gait increases cerebral activity in several brainstem structures including the pedunculopontine nucleus (PPN). The PPN is a cerebral structure known to be specifically involved in gait control in quadrupeds (Garcia-Rill, 1991), but with a less precisely defined role in humans (Bussel *et al.*, 1996; Calancie *et al.*, 1994; Pahapill and Lozano, 2000). However, we cannot exclude that our study was simply not sensitive enough to detect changes in activity in the PPN, a small brainstem structure likely masked by pulsatile MR-artefacts.

Cerebral contributions to motor imagery of precision gait

Imagining to walk along a narrow path resulted in increased cerebral activity bilaterally in the superior parietal lobule and in the right sMOG, i.e. in structures with strong sensory afferences but

without direct access to the spinal motor output. Given the role that the posterior parietal cortex plays in allocating attentional resources (Corbetta and Shulman, 2002), it might be argued that the increased SPL activity reflects differential visuo-spatial attention to the two walking paths, rather than environmental constraints on imagined gait. However, the parietal effect we report is unlikely to be driven by spatial attention per se: while spatial selective attention is known to modulate regions along the intraparietal sulcus (Corbetta and Shulman, 2002), the present effect was localized in the dorsomedial portion of the SPL. This region has been shown to incorporate proprioceptive information related to the current body position into the motor plan (de Lange *et al.*, 2006), and to be involved in integrating visual and somatosensory information into the appropriate motor coordinates required for making spatially directed movements (Andersen, 1997; Wenderoth *et al.*, 2006). Given that our task did not involve any actual movements, the observed activity cannot be related to the processing of visual and somatosensory feedback. However, following computational models based on engineering principles (Davidson and Wolpert, 2005), it has been proposed that both actual and imagined movements involve predictions of the sensory consequences of the action (Blakemore and Sirigu, 2003). During movement execution, the predicted sensory consequences are compared to the actual sensory feedback. During motor imagery, sensory predictions are generated in the absence of concurrent action production. The parietal lobe is thought to be involved in this process of the generation of sensory predictions (Blakemore and Sirigu, 2003; Wolpert *et al.*, 1998). Given that precision gait relies more on feedforward control than normal gait (Hollands *et al.*, 1995; Hollands and Marple-Horvat, 1996), we suggest that the SPL activity we observed might reflect predictions of the sensory (presumably, somatosensory) consequences of the motor plan. These predictions might take into account the width of the path, the position of the limb, and the intended walking movements. This interpretation also fits with our finding that, when a narrow path was presented, the right SPL increased its coupling with the PMd regions involved in motor imagery of gait. Crucially, our findings emphasize that these feedforward operations might become particularly relevant during precision gait. Finally, our finding is in agreement with the proposal based on cat studies that during precision walking the posterior parietal cortex is mainly involved in the planning, and the motor cortex is mainly involved in the execution of gait modifications (Drew *et al.*, 2007).

Imagining walking along a narrow path also resulted in increased cerebral activity in the superior part of the right MOG, near the EBA (Downing *et al.*, 2001). This region has been implicated in the visual perception of human body parts (Downing *et al.*, 2001), but our stimuli did not contain any body parts, and subjects had their eyes closed during imagery. We suggest that the enhanced sMOG activity during MI of walking along a narrow path reflects the generation of accurate predictions of the sensory (presumably visual) consequences of the motor plan. This interpretation fits with the finding that, when a narrow path was presented, the right sMOG increased its coupling with the premotor regions involved in motor imagery of gait. This increased coupling suggests that the sMOG activity might provide a relevant contribution to task performance, rather than being a by-product of collateral visual imagery in an allocentric perspective (Saxe *et al.*, 2006). This interpretation implies that extrastriate regions might be involved in generating visual predictions relevant to motor control (Astafiev *et al.*, 2004; Helmich *et al.*, 2007; Toni *et al.*, 2002). Given that during precision gait the subjects' gaze becomes directed downwards towards the area of foot-fall for each step (Hollands *et al.*, 1995), it appears possible that during actual motor behaviour these putative visual predictions are matched against actual visual input, analogously to what has been reported in other sensory domains (Blakemore and Sirigu, 2003; Diedrichsen *et al.*, 2005).
It might appear puzzling that an extrastriate area, rather than visually-responsive portions of the parietal cortex (like the inferior parietal lobule, IPL), is recruited for generating visual predictions of walking movements. It is possible that the IPL cannot support the control of a leg move-



Supplementary Figure 4.1 *Statistical parametric maps (p<0.05 FWE-corrected for multiple comparisons), of increased cerebral activity during motor imagery (MI) of gait (compared to visual imagery (VI), in red), and during right foot movements (i.e. increase in activity during motor response with right foot compared to motor response with left foot, in blue-cyan) superimposed on a rendered brain viewed from the top. R = right.*

ment, given that this region lacks a clear leg representation (Rizzolatti and Luppino, 2001). Yet, other studies have demonstrated the generic involvement of this region in motor imagery of gait (Malouin *et al.*, 2003; Sacco *et al.*, 2006). A more likely possibility is that the contribution of the IPL to MI of gait reflects its role in processing goals of an action (Fogassi and Luppino, 2005; Hamilton and Grafton, 2006; Majdandzic *et al.*, 2007). In our setting, imagining to walk along a narrow or a broad path requires different motor plans, but it entails the same goal ("reach the pillar"). Therefore, we speculate that the IPL supports the generation of sensorimotor predictions relative to the intended consequences of an action, whereas posterior extrastriate regions might support predictions more closely associated with the movement details.

Some cerebral regions might have been driven by the increased postural control required by gait, in particular along a narrow path. For instance, given that the cerebellum plays an important role in balance control (Morton and Bastian, 2004), that balance problems contribute to gait ataxia in patients with cerebellar lesions (Morton and Bastian, 2003), and that patients with cerebellar lesions have difficulties with tandem gait (Stolze *et al.*, 2002), it is conceivable that the trend of increased activity observed in the cerebellum might be related to the balancing component during motor imagery of gait along the narrow path. Accordingly, some subjects mentioned (during a debriefing at the end of the experiment) to have put emphasis on balancing during motor imagery of gait along the narrow path. Unfortunately, we do not have a quantitative measure to determine the relevance of imagined balancing across our group, and the reduced strength of the cerebellar effect might be related to a between-subject inconsistency. Alternatively, the weak effect in the cerebellum might be related to the fact that the main role of the cerebellum in feedforward control is to make rapid predictions of the sensory consequences of motor actions, in order to compare them with the actual sensory consequences of a movement (Blakemore and Sirigu, 2003). Our imagery task did not involve any actual movements, and therefore the cerebellum may have not been involved because it was not possible to compare the predictions to the actual sensory consequences.

Cerebral contributions to motor imagery of gait along different distances

We found that during motor imagery, cerebral activity in the cerebellum and SMA increased with increasing path length. Both these regions have been previously linked to timing functions (Halsband *et al.*, 1993; Ivry, 1996; Rao *et al.*, 1997). Therefore, it might be argued that activity in these regions is related to subjects estimating the time they would need to cover the indicated path. However, estimating the time required to cover the indicated path is required during both imagery

tasks. We found no differences in imagery time between MI and VI, and therefore the VI task allowed us to correct for these time estimation effects. We suggest that the SMA and cerebellum are involved in a timing function that is specific for motor imagery of gait, such as the timing of the walking movements.

Conclusion

Our results show that motor imagery of gait results in increased activity in the PMd, RCZp, SPL, and putamen. In addition, the increased spatial accuracy required to imagine walking along a narrow path increases cerebral activity bilaterally in the SPL and in the right SMOG, together with increased effective connectivity between these regions and the dorsal premotor areas controlling foot movements. These results emphasize the role of cortical structures outside primary motor regions in imagining gait movements when accurate foot positioning is required. Given that gait impairments in neurological disorders like Parkinson's Disease become dramatically evident when patients need to negotiate environmental constraints (for example passing a narrow door) (Giladi *et al.*, 1992), it becomes relevant to test whether these effects are related to altered responses and/or connectivity of the parietal, premotor, and extrastriate regions described in this study.

Acknowledgements

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Chapter

C5

Motor imagery of foot dorsiflexion and gait: effects on corticospinal excitability

This chapter is based on: Bakker M, Overeem S, Snijders AH, Borm G, van Elswijk G, Toni I, Bloem BR (2008). Clin Neurophysiol, 119(11), 2519-2527.

Summary

We examined how corticospinal excitability was affected by motor imagery of foot dorsiflexion and motor imagery of gait. Transcranial magnetic stimulation was applied over the primary motor cortex of 16 young healthy subjects while they performed imaginary foot dorsiflexions (Experiment I) and imaginary walking (Experiment II). Motor evoked potentials (MEPs) were recorded from the tibialis anterior (TA) and first dorsal interosseus (FDI). MEPs recorded during motor imagery were compared to those recorded during a matched visual imagery task. We found that imagined foot dorsiflexions increased MEP areas in both a task-related muscle (TA), and a task-unrelated muscle (FDI), with larger increases in the task-related muscle. Overall, imagined walking did not change MEP areas. However, subjects with larger increases in TA during imagined foot dorsiflexion also showed larger increases in TA during imagined walking. To conclude, our findings suggest that imagery of a simple lower extremity movement evokes increases in corticospinal excitability. Furthermore, corticospinal effects of a simple motor imagery task can predict corticospinal effects of a more complex motor imagery task involving the same muscle.

Introduction

Studies in cats and rodents indicate that gait is an automatic motor task regulated largely at the level of the brainstem and spinal cord (Dietz, 2003). However, the fine control of stepping movements is believed to depend on higher brain centres, including the motor cortex, which are involved in adapting walking movements to environmental and motivational demands (Armstrong, 1988). In humans, little is known about the cerebral control of gait. It has been suggested that, contrary to cats, the activation of human locomotor structures within the brainstem and spinal cord are more dependent upon cortical and subcortical inputs (Bussel *et al.*, 1996; Calancie *et al.*, 1994). Several different approaches and techniques have been used to explore the cerebral bases of human gait (for a review see Bakker *et al.*, 2007b). One such approach is to record cerebral activity during motor imagery of walking. Motor imagery involves the mental simulation of an action without its actual execution (Jeannerod, 1994; Jeannerod, 2006). The rationale behind the approach is that motor imagery and actual movements share, at least in part, common neural substrates (Porro *et al.*, 1996; Deiber *et al.*, 1998; Roth *et al.*, 1996). The majority of studies examining the cerebral structures involved in motor imagery of gait have found that motor imagery of gait increases cerebral activity in several motor cortical structures (Bakker *et al.*, 2008; Malouin *et al.*, 2003; Miyai *et al.*, 2001; Sacco *et al.*, 2006). For example, using functional magnetic resonance imaging, we found that motor imagery of gait changes activity in the dorsal premotor cortex (Bakker *et al.*, 2008). However, it remains unclear whether this increase in premotor cortical activity during imagined walking is accompanied by an increased corticospinal excitability.

One possibility to further explore this question is the use of transcranial magnetic stimulation (TMS) over the primary motor cortex, which is a widely accepted technique to examine changes in excitability of the corticospinal system (Petersen *et al.*, 2003; Reis *et al.*, 2008). Prior TMS studies on imagery have mainly focused on relatively simple hand movements, such as finger flexion-extension, finger opposition, or hand rotation. Motor imagery of both complex and simple hand movements induces a muscle-specific and temporally modulated increase in corticospinal excitability (Fadiga *et al.*, 1999; Fourkas *et al.*, 2006a; Kuhtz-Buschbeck *et al.*, 2003; Rossini *et al.*, 1999; Stinear and Byblow, 2004). For example, during imagined repetitive wrist flexion/extension movements, corticospinal excitability in the flexor muscle was larger during the phase of imagined flexion, whilst the opposite was true for the extensor muscle (Hashimoto and Rothwell, 1999). Furthermore, the increases in corticospinal excitability were not accompanied by concomitant changes in spinal excitability, as revealed by H-reflex testing (Abbruzzese *et al.*, 1996; Hashimoto and Rothwell, 1999; Kasai *et al.*, 1997). Taken together, these findings suggested that the increases in corticospinal excitability for imagined hand movements are probably mediated mainly via increased excitability of cortical circuits.

Few studies have examined changes in corticospinal excitability during motor imagery of lower limb movements (Hiraoka, 2002; Tremblay *et al.*, 2001). Tremblay *et al.* (2001) found a specific increase in corticospinal excitability of the quadriceps during motor imagery of leg extension as compared to a rest condition. Furthermore, Hiraoka (2002) found that corticospinal excitability of the soleus muscle decreased significantly during imagined stumbling, without accompanying changes in soleus H-reflex areas. To date, no study has examined changes in corticospinal excitability during a more complex lower limb task, such as motor imagery of gait.

Here, we examined whether motor imagery of a simple foot dorsiflexion (Experiment I), and motor imagery of gait (Experiment II) can modulate corticospinal excitability. We assessed the specificity of the effects by using matched visual imagery tasks. For motor imagery of foot dorsiflexion, we used a protocol that was adapted from previous TMS studies on motor imagery of

hand movements (Fourkas *et al.*, 2006a; Fourkas *et al.*, 2006b). For motor imagery of gait, we used a protocol that was adapted from our previous fMRI study on motor imagery of gait (Bakker *et al.*, 2008). This allowed us to examine whether the changes in premotor activity during motor imagery of gait observed in our fMRI experiment, were accompanied by an increase in corticospinal excitability. Furthermore, this protocol had the advantage that it was a validated motor imagery protocol that allowed us to quantify imagery of gait performance by recording imagery times (Bakker *et al.*, 2007a).

Methods

Subjects

Eighteen healthy volunteers participated after giving written informed consent according to the institutional guidelines of the Local Ethics Committee. During the preparation phase, two subjects decided not to continue with the experiment, because they experienced the TMS pulses as being too uncomfortable. The remaining 16 subjects completed the experiment (10 women, 21.6±0.4 years, mean ± SEM). All subjects had normal or corrected-to-normal vision, and were consistent right-handers (Edinburgh Handedness Inventory (Oldfield, 1971) score 84±4 %). They had no metal or electronic implants, and no history of neurological or orthopaedic disorders. Imagery ability scores as determined by the Vividness of Motor Imagery Questionnaire (Isaac *et al.*, 2009) ranged from 26 to 89 for first person imagery (51±4), and from 27 to 80 for third person imagery (56±4), which is comparable to the scores found recently in a very large group of young healthy subjects (Mulder *et al.*, 2007). All subjects participated in two experiments, first assessing imagery of foot dorsiflexion, and next assessing imagery of gait. The study was approved by the Local Ethics Committee.

Electromyography

To record electromyography (EMG), pairs of self-adhesive 10-mm diameter silver-silver chloride electrodes (Kendall-LTP, Chicopee, MA) were placed 3 cm apart along the muscle belly of right tibialis anterior (TA) and gastrocnemius (GM) muscles, and in a "belly-tendon" arrangement on the right first dorsal interosseus (FDI) muscle (FDI was taken as a reference muscle, being an intrinsic hand muscle whose corticospinal excitability does not change during gait (Schubert *et al.*, 1997). Therefore, it was expected that corticospinal excitability in this muscle would not be modulated during imagery.) EMG signals were amplified (gain 200) and filtered (2-1000 Hz) using an Ekida amplifier (Ekida GmbH, Helmstadt, Germany) before being digitized (0.76 μV/bit, 5000 Hz) by a Power 1401 data acquisition system (Cambridge Electronic Design, Cambridge, United Kingdom). Recordings of EMG data commenced 1 s prior to TMS stimuli and were collected for 2 s. Data were processed offline using MATLAB (MathWorks, Natick, MA) with FieldTrip, an open source toolbox for the analysis of electrophysiological data (http://www.ru.nl/fcdonders/fieldtrip/). The TMS pulses induced sharp peaks in the EMG recordings. Before filtering, these artefacts were cut out and the respective samples were replaced using spline interpolation. This was done to prevent expanding of the artefacts during filtering, which would create a risk of interference with the MEP. EMG was further filtered digitally (2-400 Hz) and segmented into epochs running from 100 ms before to 400 ms after each TMS pulse. We used a high-pass filter of 2 Hz instead of the more commonly used 10 Hz high-pass filter, because the 10 Hz filter-induced MEP-related filter artefacts during the period prior to the TMS pulse. To prevent that any remaining low frequency drifts influenced the data, baseline correction was performed based on the period 100 ms prior to the TMS pulse.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was applied using a custom-made angled double cone coil (wing diameter 120 mm) connected to a Magstim BiStim² stimulator (Magstim Company, Whitland, UK). Subjects wore earplugs, and a swimming cap was fitted onto the subject's head on which the vertex was marked. The crossover of the coil was positioned one centimeter left and anterior of the vertex. Stimulus intensity was set at 35% of maximum stimulator output and was then increased with steps of 5% until a motor evoked potential (MEP) was elicited in the TA. Then the coil was moved in small steps to determine the scalp position at which the MEPs in the TA were largest, i.e. the hotspot. Once the hotspot was found, the position of the coil was marked on the swimming cap, and stimulus intensity was set to the intensity that reproducibly elicited a MEP of around 0.5 – 1.0 mV peak-to-peak. On average, the stimulus intensity used was 44.6% ± 2.4 (SEM) (range: 31 – 60%) of maximal stimulator output. In the TA, the mean peak-to-peak MEP area across all trials was 0.66 ± 0.03 mV in experiment I, and 0.60 ± 0.02 mV in experiment II. While stimulating at the TA hotspot, we were able to reliably record MEPs in the FDI as well; i.e. mean peak-to-peak MEP area in the FDI was 1.44 ± 0.08 mV in Experiment I, and 1.25 ± 0.05 mV in Experiment II. We were not able to record reliable MEPs in the medial gastrocnemius muscle, peak-to-peak amplitude: 0.081 ± 0.004 mV in Experiment I, and 0.097 ± 0.005 mV in Experiment II. Therefore, we only included recordings from the TA and FDI in our analyses.

Task and procedures. Experiment I: imagined foot dorsiflexion

In the first experiment, we examined the effect of imagined foot dorsiflexion on corticospinal excitability. We always performed this experiment prior to the imagined gait experiment because imagined foot dorsiflexion is a simple motor imagery task which allowed subjects to become familiar with performing motor imagery.

Experimental set-up

Subjects were seated comfortably in a chair that was adjusted in height so that the subjects' feet rested comfortably on the floor. Written instructions were projected on a computer screen located in front of the subject. Subjects were sitting with their right leg extended. Their arms and hands were resting, pronated, on a pillow on their lap. Auditory and visual stimuli presentation was controlled through a PC running Presentation software (Neurobehavioral systems, Albany, USA). The experimenter was standing behind the subject and held the TMS coil above the TA hotspot while gently fixating the head.

Tasks

Subjects performed two tasks: motor imagery of foot dorsiflexion and visual imagery of a static foot. During motor imagery, subjects were asked to imagine a single dorsiflexion of their right foot. We instructed subjects to imagine the foot movement as vividly as possible, in a first person perspective, as if their foot was moving, but without making any actual movements. During visual imagery, subjects were asked to imagine seeing their right foot in its current static position. We again instructed subjects to imagine seeing the static right foot as vividly as possible, without making any actual movements. Subjects performed both imagery tasks with eyes closed. This was done in order to optimize imagery performance, as was done in previous studies (Fourkas *et al.*, 2006b; Hashimoto and Rothwell, 1999; Mercier *et al.*, 2008). The trial time-course was based on two previous studies examining changes in corticospinal excitability during motor imagery (Fourkas *et al.*, 2006a; Fourkas *et al.*, 2006b). An auditory cue indicated the onset of a trial. Subjects should start performing the imagery task as soon as they heard the auditory cue, a variable interval of 3–3.5 s elapsed between the beep and the TMS pulse. The TMS pulse indicated the end of a trial (for trial time course see Fig 5.1). A rest period (7 s) elapsed before the next trial.

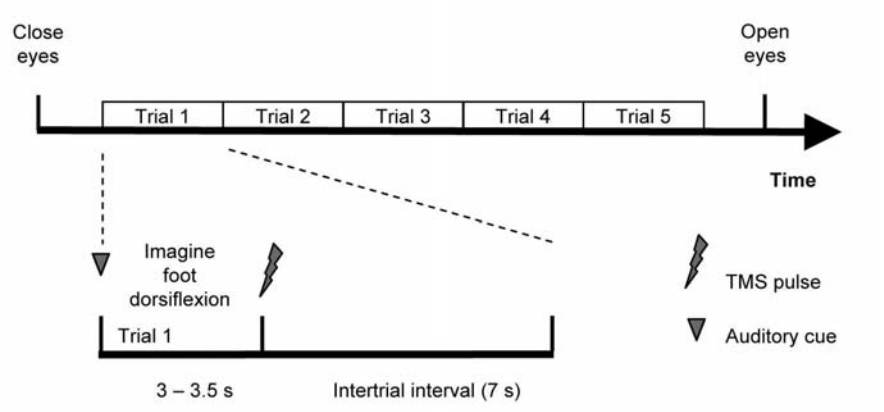

Figure 5.1 Example of a motor imagery block in experiment I. *Each block consisted of five trials. Subjects closed their eyes at the beginning of the block. Each trial started with an auditory cue indicating that subjects should start performing the imagery task. After a variable interval of 3-3.5 s a TMS pulse was delivered. Subjects were instructed to stop performing the imagery task after the TMS pulse had been delivered. A rest period of 7 s elapsed before the onset of the next trial. After five trials, the block was finished, and the experimenter indicated that subjects could open their eyes.*

Experimental procedures

The experiment was divided into two motor imagery blocks and two visual imagery blocks of five trials each (2 blocks × 2 tasks (motor imagery, visual imagery) × 5 trials = 20 trials), with a rest period of 7 s in between successive trials, and a rest period of several minutes in between successive blocks. Subjects closed their eyes at the beginning of each block. Subjects were allowed to open their eyes at the end of the block when the experimenter indicated that the block had finished. The motor imagery and visual imagery blocks were performed alternately, and the order was counterbalanced across subjects. Before we started the experiment, subjects were given written instructions explaining both tasks, followed by actual performance of the foot movement, and a training of both imagery tasks (three trials for each task, with TMS pulses). Prior to each block, subjects were instructed which task they should perform in the next block.

Tasks and procedures. Experiment II: imagined gait

In the second experiment, we examined the effect of imagined gait on corticospinal excitability.

Experimental set-up

Experiment II was performed directly after experiment I, and subjects remained seated in the same chair. Therefore, the experimental set-up of Experiment II was largely similar to that of Experiment I, with two differences. First, subjects did not extend their right leg during Experiment II. Second, button presses with the left thumb were recorded to measure behavioural responses.

Tasks

We used the same protocol as in our previous fMRI study (Bakker *et al.*, 2008), which is a validated protocol that allows for quantifying motor imagery of gait performance by recording imagery times (Bakker *et al.*, 2007a). We asked subjects to imagine walking along visually presented paths

of two different widths (9, 27 cm) and three different distances (6, 8 and 10 m) that evoked either normal walking (broad path) or exact foot placement and increased postural control (narrow path). This manipulation allowed us to isolate the effects of movement distance and movement difficulty on imagined walking times. During a matched visual imagery task, subjects imagined a disk moving along the same paths and distances used in the motor imagery task. Both tasks started with the presentation of a photograph showing a corridor with a path in the middle (see Fig 5.2 - the stimuli have been described in detail previously, see also Bakker *et al.*, 2007a). During motor imagery trials, a green square marked the beginning of the path in the photograph. Subjects were asked to inspect the photograph on display, to close their eyes, and to imagine walking along the path, starting from the green square and stopping at the green pillar. We instructed subjects to imagine the walking movement as vividly as possible, in a first person perspective, as if their legs were moving, but without making any actual movements. During visual imagery trials, a black disk was present at the beginning of the path in the photograph. Subjects were asked to inspect the photograph, to close their eyes, and to imagine seeing the black disc moving along the path, from its starting position until the green pillar. We again instructed subjects to imagine the movement as vividly as possible, without making any actual movements. During both tasks, the path could have two different widths (narrow, broad). In addition, the green pillar could be placed at three different distances from the green square or the black disc (6, 8 and 10 m). During each trial, subjects signalled that they had started and stopped the imagery by pressing a button. The time between the two button presses was taken as imagery time (see Fig. 5.2 for trial time course). A TMS pulse was delivered at 1.7 - 3 s after the first button press in each trial. This time interval was chosen to make sure that the TMS pulse would be delivered before the end of the trial in all subjects. The time-interval was based on behavioural results of our previous fMRI experiment (Bakker *et al.*, 2008). Subjects were instructed to continue with the imagery task after the TMS pulse had been delivered (this was necessary to be able to record imagery times).

Experimental procedures

The experiment was divided into two motor imagery blocks and two visual imagery blocks of 10 trials each (2 blocks × 2 tasks (motor imagery, visual imagery) × 2 path widths (narrow, broad) × 5 trials = 40 trials), with breaks of several minutes between successive blocks. The motor imagery and visual imagery blocks were performed alternately, and the order was counterbalanced across subjects. Prior to each block, subjects were instructed which task they should perform in the next block. In between trials a fixation cross was presented on the screen (inter-trial interval, ITI: 7.0 - 7.5 s).

Prior to the first and second block, subjects were given written instructions about the task they would perform in the next session, followed by training in the relevant task (15 trials, no TMS pulses during training). Prior to the beginning of Experiment I subjects physically walked along short versions (three meters) of both the broad and the narrow paths (three times for each path width), at a comfortable pace, avoiding to place their feet outside the path. This was done to make subjects familiar with the kinaesthetic feeling of walking along the different paths. The broad path allowed for walking over the path with a normal gait, whereas the narrow path required the subjects to carefully position their feet one in front of the other. We instructed subjects to pay attention to the feeling of walking along the different path widths, and to imagine walking in a similar way along the two different paths during the imagery trials. To make subjects familiar with the movement of the disc, they were made to see a video of the disc moving through the same corridor as in the photographs, but without a linoleum path in the middle of the corridor. The disc moved for 6 m, in a straight line, at a uniform speed of about 0.8 m/s. We instructed subjects to imagine seeing the disc moving in a similar way along the two different paths during the imagery trials.

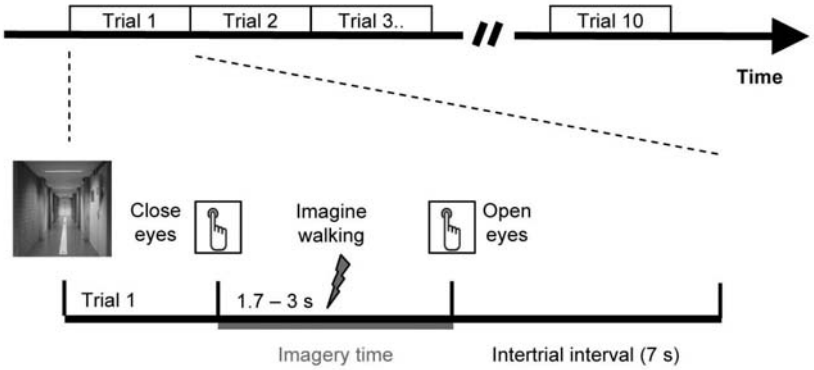

Fig. 5.2 Example of a motor imagery block in experiment II. *Each block consisted of 10 imagery trials. During each trial, after a short inspection of the photograph on display, the subjects closed their eyes and imagined standing on the left side of the path, next to the green square. The subjects were asked to press a button with the index finger of their right hand to signal that they had started imagining to step onto the path and walking along the path. The subjects were also instructed to press the button again when they imagined that they had reached the end of the walking trajectory. A TMS pulse was delivered at 1.7 - 3 s after the first button press in each trial. Following the second button press, subjects could open their eyes, and a fixation cross was presented on the screen (inter-trial interval, ITI: 7 sec).*

Behavioural data analysis

In Experiment I we did not record any behavioural data. In Experiment II, we examined the effects of our experimental manipulations on imagery times in order to quantify task performance. We measured the time between the two button presses that marked the start and the end of the imagined visual or walking movements (imagery time, see Fig. 5.2). We used a Mixed Model to analyze the effects of our experimental manipulations on imagery times. We included imagery time as the dependent variable, and SUBJECT as a random factor. As fixed covariates, we included TASK (motor imagery and visual imagery), PATH WIDTH (broad and narrow), PATH LENGTH (6, 8 and 10 m), TASK × PATH WIDTH, and TASK × PATH LENGTH. In addition, we performed a Mixed Model analysis for each task separately. Imagery time was again included as a dependent variable, SUBJECT as a random factor, and PATH WIDTH and PATH LENGTH as fixed covariates. All independent variables were rescaled in such a way that their mean value was 0. Because of this, the coefficient of the main effect estimated the mean differences between the various conditions, even if interactions were included in the model.

EMG data analysis

We used MEP area as our primary outcome measure, because TA MEPs were predominantly polyphasic. MEP area was quantified for each trial as the area on rectified EMG responses in a fixed time interval of 15-80 ms after the TMS trigger (see Fig. 5.3). As a secondary research question we examined whether the target muscle was at rest at the time of TMS. Background EMG activity was calculated for each TMS trial as the root-mean-square (RMS) amplitude of the 105 to 5 ms pre-TMS EMG trace.

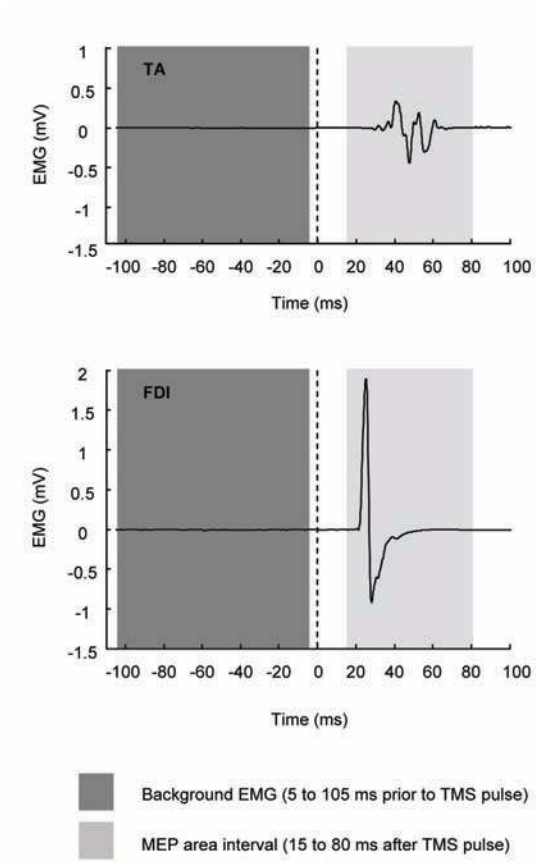

Fig. 5.3 Motor evoked potentials. *Examples of motor evoked potentials (MEPs) recorded in the first dorsal interosseus (FDI), and tibialis anterior (TA) in a single subject during a single trial. The dashed line indicates the moment at which the TMS pulse was given (the TMS artefact has been removed from the EMG trace as reported in the Methods section). The dark grey block indicates the 100 ms interval that was used to calculate the background electromyography (EMG) activity. The light grey block indicates the 65 ms interval that was used to calculate the MEP area.*

Statistical analysis. Experiment I: Imagined foot dorsiflexion

For the statistical analysis of MEP areas, all MEP areas were transformed (natural log) to address non-normality. We used a Mixed Model to analyze the effects of our experimental manipulations on MEP area. We included MEP area as the dependent variable, and SUBJECT as a random factor. As fixed covariates we included TASK (motor imagery and visual imagery), MUSCLE (TA and FDI), TASK × MUSCLE, BACKGROUND EMG, and BACKGROUND EMG × MUSCLE. We included background EMG in the mixed model, because muscle contraction increases MEP areas (Hess *et al.*, 1986). Including background EMG in the mixed model allowed us to correct for possible differences in background EMG levels (Bloem *et al.*, 1993). In addition to the overall analysis, we also performed a Mixed Model analysis for each muscle separately, using the same variables. For all analyses, independent variables were rescaled in such a way that they had mean 0. The alpha-level of all statistical analyses was set at $p < 0.05$.

The statistical analysis of background EMG was largely similar to that of MEP areas with the only difference that background EMG was set as the dependent variable, and we did not include BACKGROUND EMG, and BACKGROUND EMG × MUSCLE as fixed covariates in the model.

Statistical analysis. Experiment II: Imagined gait
The statistical analysis of experiment II was largely similar to that of experiment I, with the following differences. For the overall Mixed Model, we also included the factors PATH WIDTH (broad and narrow), TASK × PATH WIDTH and TASK × PATH WIDTH × MUSCLE as fixed covariates. For the muscle specific Mixed Models, we also included the factors PATH WIDTH (broad and narrow), and TASK × PATH WIDTH as fixed covariates. Path length was solely varied to have a behavioural control of whether subjects accurately performed imagery (Bakker *et al.*, 2007a). Therefore we pooled across the factor path length for the EMG analysis.

Statistical analysis. Experiment I versus II: Imagined foot dorsiflexion versus imagined gait
Finally, we examined the relationship between the effects of imagined foot dorsiflexion (Experiment I) and imagined walking (Experiment II) on MEP areas. First, we used a Mixed Model to calculate the effect sizes of imagined foot dorsiflexion and imagined walking on MEP area in each subject and muscle separately. In this mixed model analysis, we included MEP area as the dependent variable, and TASK (motor imagery and visual imagery) and BACKGROUND EMG as fixed covariates. Afterwards, we used a linear regression analysis to examine for each muscle (TA and FDI) the relationship between effect sizes of imagined foot dorsiflexion and imagined walking. We included single-subject effect sizes of imagined foot dorsiflexion on MEP areas as independent variable in the linear regression, and single-subject effect sizes of imagined walking on MEP areas as dependent variable.

Results

Experiment I: motor imagery of foot dorsiflexion

MEP area
The mean MEP areas for each task and muscle are presented in Table 5.1. MEP areas were larger during imagined foot dorsiflexion compared to visual imagery (effect size [95% confidence interval] = 38% [19% to 60%], p<0.001). Interestingly, this effect was observed in both muscles (Fig. 5.4). In the TA, imagined foot dorsiflexion resulted in 57% [37% to 80%] larger MEP areas (p<0.001). In the FDI, imagined foot dorsiflexion resulted in a relatively smaller increase in MEP areas of 18% [4% to 34%], but this was still significant (p=0.01). The effect of task on MEP areas was 26% [0% to 45%] larger for the TA than for the FDI (TASK × MUSCLE interaction: p=0.05). These findings suggest that motor imagery of foot dorsiflexion increased corticospinal excitability in both a task-related muscle (TA), and a task-unrelated muscle (FDI). However, the increase in the task-related muscle was larger than the effect in the task-unrelated muscle.

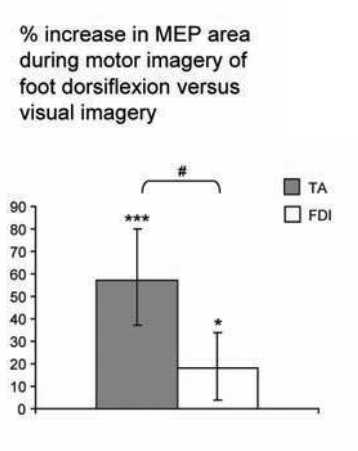

Fig. 5.4 Effects of imagined foot dorsiflexion on MEP area. *Percentage increase of MEP area during motor imagery of foot dorsiflexion compared to visual imagery of a static foot in the TA and FDI. Data represent effect size ± 95% confidence intervals. #P=0.05, *P<0.05, ***P < 0.001.*

Background EMG
Background EMG activity was low in both muscles (Table 5.1). Imagined foot dorsiflexion did not significantly influence background EMG activity compared to

visual imagery (0% [-5% to 7%], p=0.89). In addition, the effect of imagined foot dorsiflexion on background EMG was not different for the different muscles (TASK × MUSCLE interaction: 8% [-4% to 18%], p=0.22).

Table 5.1. MEP areas and background EMG

			MEP area (mV*ms)		Background EMG (μV)	
Experiment	**Muscle**	**Task**	**mean**	**SEM**	**mean**	**SEM**
I	TA	Motor imagery of foot dorsiflexion	5.22	1.17	1.72	0.11
		Visual imagery of static foot	2.84	0.51	1.68	0.14
	FDI	Motor imagery of foot dorsiflexion	6.34	1.62	1.73	0.17
		Visual imagery of static foot	5.50	1.33	1.93	0.29
II	TA	Motor imagery of gait	3.61	0.59	1.69	0.13
		Visual imagery of disc	3.18	0.47	1.71	0.11
	FDI	Motor imagery of gait	5.25	1.29	2.03	0.22
		Visual imagery of disc	4.76	1.22	1.79	0.15

EMG: electromyography, FDI: first dorsal interosseus, SEM: standard error of mean, TA: tibialis anterior

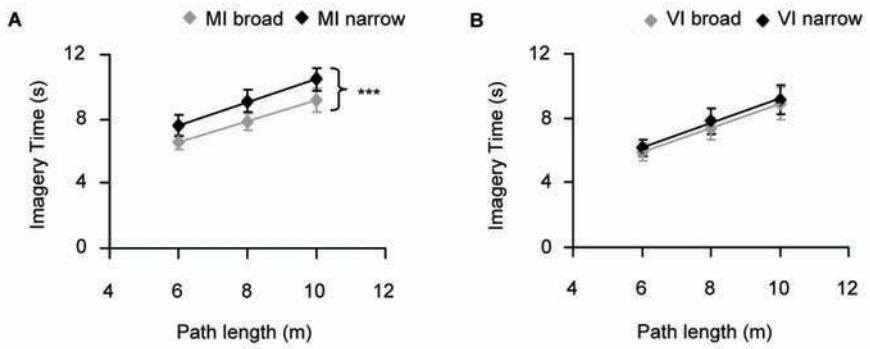

Fig. 5.5 Behavioural results of experiment II. *Imagery times (IT) are shown for each of the three different path lengths (6, 8, and 10 m), and the two different path widths [Broad (27 cm), and Narrow (9 cm)], separately for each of the two tasks [**A)** motor imagery of gait (MI), and **B)** visual imagery of a moving disc (VI)]. Data represent mean ± SEM. ***P < 0.001. It can be seen that the effect of path width on imagery times differed for the different tasks (TASK × PATH WIDTH interaction: p<0.01). These results indicate that motor imagery was sensitive to the environmental constraints imposed by a narrow walking path, whereas visual imagery was not. These findings suggest that subjects complied with the imagery tasks.*

Experiment II: motor imagery of gait

Behaviour
We recorded imagery times in order to quantify imagery performance (Bakker *et al.*, 2007a). Imagery times were longer with increasing path length (effect size [95% confidence interval] = 0.7 s [0.6 s to 0.8 s], $p<0.001$ – Fig. 5.5), and this effect was not different for the different tasks (TASK × PATH LENGTH interaction: $p=0.42$). Furthermore, the effect of path width on imagery times differed for the different tasks (TASK × PATH WIDTH interaction: 0.9 s [0.4 s to 1.4 s], $p<0.01$). During imagined walking a smaller path width increased imagery times with 1.2 s ([1.5 s to 0.9 s], $p<0.001$, Fig. 5.5A), whereas during visual imagery a smaller path width increased imagery times with only 0.3 s ([0 s to 0.7 s], $p=0.06$, Fig. 5.5B). These results indicate that motor imagery was sensitive to the environmental constraints imposed by a narrow walking path that allows only for positioning one foot at a time on the path, whereas visual imagery only tended to be affected. These data suggest that subjects complied with the imagery tasks.

MEP area
The mean MEP areas for each task and muscle are presented in Table 5.1. Overall, imagined walking did not significantly influence MEP areas compared to visual imagery (6% [-4% to 17%], $p=0.25$). Furthermore, there was no significant difference between the effect of imagined walking on MEP areas in TA versus FDI (TASK × MUSCLE interaction: 2% [-16% to 25%], $p=0.83$). Finally, there was no effect of path width on MEP areas during imagined walking (PATH WIDTH: $p=0.17$; TASK × PATH WIDTH: $p=0.77$; TASK × PATH WIDTH × MUSCLE; $p=0.73$). These findings suggest that motor imagery of walking did not influence corticospinal excitability compared to visual imagery.

Background EMG
Background EMG activity was low in both muscles (Table 5.1). The effect of imagined walking on background EMG activity was different for the two muscles (TASK × MUSCLE interaction, 13% [3% to 24%], $p=0.01$). In the TA, imagined walking had no significant effect on background EMG activity (0% [-6% to 4%] ($p=0.70$)). In the FDI, imagined walking did significantly increase background EMG activity (12% [5% to 20%] ($p<0.01$)). We found no effects of path width on background EMG during imagined walking (PATH WIDTH: $p=0.88$; TASK × PATH WIDTH: $p=0.20$; TASK × PATH WIDTH × MUSCLE; $p=0.36$).

Foot dorsiflexion versus gait
For each individual and each muscle, we calculated the effect size of imagined foot dorsiflexion and imagined gait on MEP areas. We examined whether there was a linear relationship between the effect sizes of imagined gait and the effect sizes of imagined foot dorsiflexion. The effect of imagined gait on TA MEP areas was positively correlated with the effect of imagined foot dorsiflexion on TA MEP areas ($r = 0.56$, $p=0.024$) (Fig. 5.6). In other words, subjects with larger effects of imagined foot dorsiflexion on TA MEP areas also showed larger effects of imagined gait. The correlation was specific for the TA, as we found no correlations between (a) the effects of imagined gait on FDI MEP areas and the effect of imagined foot dorsiflexion on FDI MEP areas ($r = -0.09$), and (b) the effect of imagined gait on FDI MEP areas and the effects of imagined foot dorsiflexion on TA MEP areas ($r = 0.01$). We found no relationship between vividness of motor imagery (determined by questionnaire) and the effect of imagined foot dorsiflexion on TA MEP areas ($r=0.39$, $p=0.14$). We did find a trend for a positive relationship between the average MEP area per subject and the effect of imagery of foot dorsiflexion on TA MEP areas ($r=0.47$, $p=0.07$).

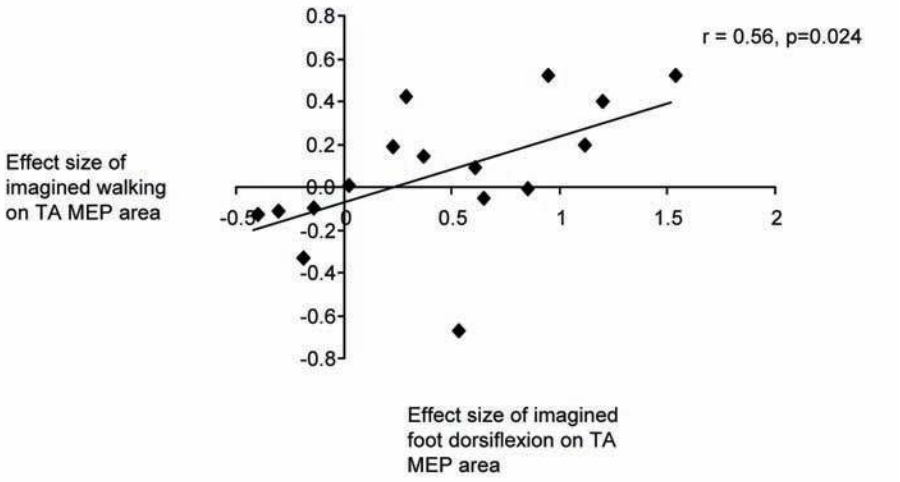

Fig. 5.6 Relationship between effects of imagined foot dorsiflexion and imagined gait on MEP area in the TA. *Effect size of imagined gait on MEP area in the TA is plotted against the effect size of imagined foot dorsiflexion on MEP area in the TA for each subject. Line represents linear regression curve. It can be seen that subjects with larger effects of imagined foot dorsiflexion on MEP areas in the TA also showed larger effects of imagined gait.*

We performed a post-hoc analysis on those five subjects in which the effect sizes of imagined foot dorsiflexion on TA MEP areas were larger than 0.75. In those subjects, imagined walking increased MEP areas by 29% [8% to 52%] ($p<0.01$). Although the effect size of imagined walking was larger for TA (38%) than for FDI (14%), this difference was not significant, as we found no significant TASK x MUSCLE interaction ($p=0.10$). These findings show that, contrary to the whole group of subjects, this selection of subjects did show an effect of imagined walking on corticospinal excitability. However, it remains to be seen whether this effect is specific for the TA.

Discussion

In this study, we examined the effects of motor imagery of foot dorsiflexion and motor imagery of gait on corticospinal excitability. There were two main findings. First, imagined foot dorsiflexion increased corticospinal excitability in both the TA and the FDI, with a larger effect in the TA. This result indicates that motor imagery of a straightforward lower limb movement (foot dorsiflexion) increases corticospinal excitability in both a task-related muscle (TA) and a task-unrelated muscle (FDI), with larger increases in the task-related muscle. Second, when taking all subjects together, imagined walking did not change MEP areas. However, the size of increment of corticospinal excitability in the TA during imagined foot dorsiflexion predicted the size of the increment of corticospinal excitability in the TA during imagined gait (i.e. subjects with a larger increment of corticospinal excitability in the TA during imagined foot dorsiflexion also showed a larger increment of corticospinal excitability in the TA during imagined walking). This observation suggests that corticospinal effects of a simple imagery task can predict corticospinal effects of a more complex motor imagery task involving the same muscle. We will next discuss these findings in more detail.

Motor imagery of foot dorsiflexion

Motor imagery of foot dorsiflexion increased corticospinal excitability in both the TA and FDI, with larger effects in the TA. The finding of a larger gain in corticospinal excitability in the TA is in agreement with previous work showing that corticospinal excitability specifically increases within muscles involved in the imagined movement. This was shown during motor imagery of upper limb movements (Facchini *et al.*, 2002; Fourkas *et al.*, 2006a; Kuhtz-Buschbeck *et al.*, 2003; Stinear and Byblow, 2004) and upper leg movements (Tremblay *et al.*, 2001). Our study extends these findings by showing that corticospinal excitability is also increased during motor imagery of movements involving the lower leg. The increase in corticospinal excitability could not be explained by overall changes in background muscle activity. However, since we did not measure concurrent changes in H-reflexes, we cannot rule out the possibility that changes in spinal excitability may have contributed to the results. Note that other investigators found no H-reflex changes with motor imagery (Abbruzzese *et al.*, 1996; Hashimoto and Rothwell, 1999; Kasai *et al.*, 1997).

The finding of increased corticospinal excitability in the FDI during imagined foot dorsiflexion conflicts with previous studies showing that motor imagery only modulates corticospinal excitability of muscles specifically involved in the imagined movement, and does not modulate corticospinal excitability of muscles not involved in the imagined movement (Fourkas *et al.*, 2006a; Hashimoto and Rothwell, 1999). For example, motor imagery of wrist flexion-extension movements modulates MEP areas in flexor carpi radialis and extensor carpi radialis muscles, but does not modulate MEP areas in the FDI (Hashimoto and Rothwell, 1999). Our results show that motor imagery of simple lower leg movements does not only influence corticospinal excitability of a task-related muscle (TA), but also influences corticospinal excitability of a task-unrelated muscle (FDI). One might argue that the effect in the task-unrelated upper limb muscle might be related to interlimb coordination. However, changes in corticospinal excitability of upper limb muscles during lower limb movements have been demonstrated mainly for wrist flexors and extensors (see for example Borroni *et al.*, 2004). In our study, we found changes in corticospinal excitability in the FDI, which is an intrinsic hand muscle. One previous study has also found that imagined foot dorsiflexion can specifically modulate corticospinal excitability of intrinsic hand muscles (Marconi *et al.*, 2007). However, whereas we found *increased* corticospinal excitability of hand muscles during imagined foot dorsiflexion, Marconi *et al.* (2007) found *reduced* corticospinal excitability. One possible explanation for this discrepancy might be differences in the TMS stimulation protocol used. Whereas we stimulated at the TA hotspot using a non-focal double cone coil, Marconi *et al.* (2007) stimulated at the hotspot of a hand muscle using a more focal figure-of-eight coil. Another possible explanation might be differences in the examined hand muscles. Whereas we examined the FDI, Marconi *et al.* (2007) examined the opponens pollicis and the adbductor digiti minimi. This discrepancy remains to be explained, but both studies do suggest that motor imagery of lower limb movements can influence corticospinal excitability of intrinsic hand muscles.

Motor imagery of gait: behavioural performance

The procedures used in this study were designed to isolate specific effects of first person kinaesthetic motor imagery of gait. We recorded imagery times on a trial by trial basis, showing that imagery times increased as a function of path length during both imagined gait and visual imagery. In addition, we showed that imagery times increased as a function of path width during the imagined gait trials, but not during the visual imagery trials. This result indicates that motor imagery was sensitive to the environmental constraints imposed by a narrow walking path that allows only for positioning one foot at a time on the path. Furthermore, the motor imagery of gait task

was adapted from a previous study showing that performance of motor imagery, but not visual imagery, was influenced by subjects' body posture (Stevens, 2005). Taken together, these findings provide evidence that subjects solved the task by using first person kinaesthetic imagery.

Motor imagery of gait: corticospinal excitability

Motor imagery of walking did not result in an overall increase in corticospinal excitability as we had expected based on our previous fMRI study (Bakker *et al.*, 2008). In that fMRI experiment, we found that motor imagery of walking increased cerebral activity in the caudal part of the dorsal premotor cortex, and that this activity was anatomically distinct from that observed in the premotor cortex during motor imagery of hand rotations. Accordingly, we expected that this increased activity would result in a specific increase in corticospinal excitability of the TA. There might be several reasons for the fact that we did not find this increase in corticospinal excitability when taking all subjects together.

First, the activations found in the premotor cortex during motor imagery of gait in our previous fMRI study might be an epiphenomenon, rather than being functionally relevant for that task. However, this possibility appears unlikely, given the large body of evidence supporting the involvement of premotor cortices in motor imagery processes (for a recent review see de Lange *et al.*, 2008).

Second, imagery performance may have been better in our fMRI study compared to our TMS study. During the TMS experiment, imagined walking was performed in a sitting posture, which - because of the flexed knees - might be less suitable for motor imagery of gait than the recumbent posture that was used during the fMRI experiment. Previous work showed that motor imagery increases corticospinal excitability when body posture is compatible with the imagined movement, but not when body posture is incompatible with the imagined posture (Fourkas *et al.*, 2006a; Vargas *et al.*, 2004). Furthermore, the TMS pulses may have been perceived as uncomfortable, rendering it more difficult for subjects to remain focused on the imagery task during the TMS experiment. However, we recorded behavioural data to quantify task performance that suggest that subjects were able to perform the imagery tasks during both the TMS and fMRI experiment.

Third, the timing of our TMS pulses may not have been optimal to detect changes in corticospinal excitability. During actual walking, the TA is mainly activated during the swing phase and landing phase of walking, and the most convincing evidence for involvement of the motor cortex in controlling the TA during walking was obtained for the swing phase of walking (Petersen *et al.*, 2001). Our motor imagery of gait protocol did not allow for keeping track of the phases of the imagined walking movements. Therefore, the delivery of the TMS pulses was not linked to a particular phase of the gait cycle.

Finally, the increases in cerebral activity in the premotor cortex as recorded during the fMRI experiment may have not been strong enough to result in detectable changes in TA corticospinal excitability. TMS was applied over the primary motor cortex, whereas the changes in cerebral activity were located in the premotor cortex.

Relationship between foot dorsiflexion and walking

The experimental set-up was not designed to directly compare the effects of imagined foot dorsiflexion and imagined walking on corticospinal excitability. This would have required the tasks to be more adequately matched (e.g. for differences in trial time-course see Fig 5.1 & 5.2), and the task order to be counterbalanced across subjects. However, because the two tasks were performed by

the same subjects, the set-up did allow for examining the relationship between the effects of the two different tasks on corticospinal excitability. We found a positive relationship between the effect of imagined foot dorsiflexion and the effect of imagined walking on TA corticospinal excitability (i.e. subjects with larger increases in corticospinal excitability in the TA during imagined foot dorsiflexion also showed larger increases in corticospinal excitability in the TA during imagined walking). This relationship is interesting, since it suggests that imagined walking only influences corticospinal excitability in those subjects with the largest increment of corticospinal excitability in the TA during imagined foot dorsiflexion. The nature of this relationship remains to be determined. One possibility could be differences in general increases in corticospinal excitability across subjects. However, this is not likely given that the relationship was only found for the TA, and not for the FDI. A second possibility could be differences in imagery ability across subjects. However, there were no significant relationships between vividness of motor imagery (determined by questionnaire) and the effects of imagined foot dorsiflexion or imagined walking on TA MEP areas. A third possible explanation might be differences in MEP areas in TA across subjects. We indeed found a trend for a positive relationship between the average MEP area per subject and the effect of imagined foot dorsiflexion on MEP areas in TA ($r=0.47$, $p=0.07$). A similar relationship was not found for the FDI. This would suggest that subjects with greater TA MEP areas tend to show greater effects of motor imagery of lower leg movements on corticospinal excitability. However, this might only partially explain the relationship between the effects of imagined foot dorsiflexion and imagined walking. An additional explanation might involve differences in the extent to which subjects specifically focused on movements of the TA during imagery. In our study imagined foot dorsiflexion was always performed prior to imagined walking. Therefore, only those subjects who could specifically focus on the TA during the simple foot dorsiflexion task may have been able to also focus on this muscle during imagined walking. This would be in agreement with the fMRI finding that activity in bilateral cortical motor areas during motor imagery of gait is expanded when subjects are trained to focus their attention on the leg movements involved in walking (Sacco *et al.*, 2006).

Conclusions

Our results show that imagery of a simple lower extremity movement (foot dorsiflexion) can increase corticospinal excitability in both a task-related muscle (TA) and a task-unrelated muscle (FDI), with greater increases in the task-related muscle. These results provide further evidence for the effect of motor imagery of lower limb movements on corticospinal excitability. Furthermore, we show that imagined gait only increases corticospinal excitability in those subjects with the largest increases in corticospinal excitability during imagined foot dorsiflexion. These results suggest that corticospinal effects of a simple imagery task can predict corticospinal effects of a more complex imagery task involving the same muscle.

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Chapter

C6

Cerebral circuits underlying planning of gait in Parkinson's disease: a motor imagery study

This chapter is based on: Bakker M, Leunissen I, Overeem S, Snijders AH, Helmich RC, van Oosten RV, Bloem BR, Toni I. Submitted.

Summary

The neural mechanisms and circuitry underlying gait problems in Parkinson's disease (PD) remain largely unclear. Here, we aimed at identifying those portions of the motor system supporting gait that are altered in PD patients. More specifically, motor imagery was used as a tool to investigate alterations in neural activity related to planning of gait in PD. We recorded cerebral activity with functional magnetic resonance imaging in 19 PD patients and 21 matched healthy controls. Subjects were instructed to perform a previously validated protocol including a motor imagery of gait task and a matched visual imagery task. We objectively monitored task performance by examining the effects of motor imagery of walking on supports of different width and length on imagery times, and by recording electromyography during scanning. In addition, actual gait parameters were quantified using an electronic pressure-sensitive walkway. During actual walking, patients had a smaller step length than controls. During imagery of walking, patients and controls were equally sensitive to the constraints associated with walking on supports of different width and length. Cerebrally, PD patients showed a relative decrease in motor imagery-related activity in the bilateral supplementary motor area (SMA), in the superior parietal lobule, and in cerebellar lobule IV, as well as a relative increase in the mesencephalic locomotor region. Furthermore, SMA activity was positively correlated with step length, as measured during actual walking. These findings indicate that, in PD patients, both fronto-striatal and parieto-cerebellar circuits fail to support gait-related control mechanisms, while emphasizing altered responses of brainstem locomotor centres in PD. It remains to be seen whether these altered brainstem responses compensate for, or exacerbate gait disturbances in PD.

Introduction

Gait disturbance is one of the cardinal symptoms in patients with Parkinson's disease (PD). It is characterized by shuffling of the feet with a reduced step height and a diminished step length, leading to slowness of walking (hypokinetic gait) (Morris *et al.*, 1994; Snijders *et al.*, 2007). Gait disturbance in PD is associated with an increased risk of falls and loss of independence (Boonstra *et al.*, 2008; Rahman *et al.*, 2008). Treatment remains difficult for most patients (Boonstra *et al.*, 2008), and development of new therapies is hampered by the current lack of insight into the neural mechanisms and circuitry underlying hypokinetic gait in PD.

Several approaches have been used to improve our understanding of the pathophysiology underlying gait impairment in neurological disorders such as PD. A traditional neurological approach involved the clinical description of gait in patients with focal lesions in the central nervous system. Important observations included the recognition of a hypokinetic gait in patients with lesions in the SMA (Chung *et al.*, 2004) and in patients with a focal lesion restricted to the presumed area of the mesencephalic locomotor region (MLR) (Kuo *et al.*, 2008; Masdeu *et al.*, 1994).

Another approach involves the use of functional neuroimaging. Functional neuroimaging of gait is not straightforward, since techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) require that subjects do not move their head during sampling of task-related cerebral activity. This limitation has been circumvented by using nuclear neuroimaging techniques and radioisotopes with a relatively long half-life (Hanakawa *et al.*, 1999b; Hanakawa *et al.*, 1999a; Ouchi *et al.*, 2001). This approach allows one to quantify cerebral activity after a period of physical gait performance. For example, using HMPAO-SPECT it was found that PD patients showed less cerebral activity than controls in a left medial frontal area, right precuneus, and in the left cerebellar hemisphere (Hanakawa *et al.*, 1999b). Increased activity was found in the left temporal cortex, right insula, left cingulate cortex and cerebellar vermis. Another study investigated changes in dopamine transporter (DAT) availability during standing and during gait in unmedicated PD patients and in normal subjects using PET. That study points to alterations in the availability of DAT in the medial striatum as a source of pathophysiological changes in gait performance in PD patients. Other studies have used cerebral metabolism at rest as a local index of altered neural activity, focusing on one specific gait problem in PD, namely freezing of gait (Bartels *et al.*, 2006). During freezing of gait, patients experience brief and sudden episodes of ineffective stepping, during which their feet subjectively become 'glued to the floor' (Nieuwboer and Giladi, 2008). Comparing PD patients with and without freezing of gait revealed reduced uptake of both FDG and FDOPA in the caudate nucleus, while in the putamen there was reduced FDOPA uptake with increased FDG uptake. Furthermore, freezing patients showed decreased FDG uptake in the parietal lobe. Taken together, these studies suggest that several cerebral regions can be associated with the hypokinetic gait disorder seen in patients with PD. However, given that those studies have mainly focused on cerebral activity evoked during gait execution or during rest, it remains unclear to what extent those results are related to altered motor planning (Rosin *et al.*, 1997; Vidailhet *et al.*, 1993), impaired somatosensory processing (Almeida *et al.*, 2005) or differences in execution of gait between experimental groups. Distinguishing these different factors appears crucial for understanding motor deficits in PD. For instance, it has been shown that PD motor symptoms can be ascribed – at least in part – to difficulties in processing and integrating proprioceptive feedback signals (Abbruzzese and Berardelli, 2003; Boecker *et al.*, 1999; Rickards and Cody, 1997). Furthermore, electrophysiological correlates of cortical processing in PD patients are altered during motor preparation rather than movement execution (Cunnington *et al.*, 1997).

The goal of this study was to identify those portions of the motor system that are impaired in PD patients during the planning of gait. An established tool for examining human motor planning is motor imagery (de Lange *et al.*, 2008; Jeannerod, 1994). Motor imagery involves mentally simulating a given action without actually performing it. Imaging a movement relies on neural processes partly similar to those evoked while performing the same movement. This correspondence has been documented both in healthy controls (Deiber *et al.*, 1998; Lang *et al.*, 1994; Porro *et al.*, 1996) and in PD patients (Dominey *et al.*, 1995; Helmich *et al.*, 2007). For instance, asymmetrically affected PD patients are slower in imagining moving their more affected hand (Dominey *et al.*, 1995; Helmich *et al.*, 2007). More generally, it has been suggested that the internal simulation of an action, as evoked during motor imagery, constitutes the core element of a motor plan (Jeannerod, 1994). Accordingly, motor imagery can be used to study the cerebral properties of movement representations independently from motor output and sensory feedback (de Lange *et al.*, 2005).

Several studies have used motor imagery to examine the cerebral structures involved in the planning of gait in healthy subjects (see for example Bakker *et al.*, 2008; Jahn *et al.*, 2004; Jahn *et al.*, 2008; Malouin *et al.*, 2003; Miyai *et al.*, 2001). For example, in a recent study we localized motor imagery of gait-related increases of cerebral activity to the bilateral dorsal premotor cortex, superior parietal lobule, anterior cingulate cortex, and putamen (Bakker *et al.*, 2008). Motor imagery of gait has also been shown to increase cerebral activity in brainstem locomotor regions such as the MLR (Jahn *et al.*, 2008). Here, we capitalize on this novel approach to the study of gait control in order to isolate gait-related cerebral alterations in PD patients, independently from changes in motor execution or somatosensory processing. Accordingly, we have used functional magnetic resonance imaging (fMRI) to compare cerebral activity evoked in PD patients and healthy age-matched controls during performance of motor imagery of gait, relating changes in cerebral activity to the actual gait pattern of each subject.

Methods

Subjects

Nineteen patients with idiopathic Parkinson's Disease were studied (Table 6.1). Patients were diagnosed according to the UK Parkinson's Disease Society Bank clinical criteria by an experienced movement disorders specialist (BRB). Dopaminergic medication (levodopa or dopamine-agonists) was used by all patients, except for patient 12. Patients were without medication for at least 12 hours during the experiment (i.e. in a practically defined "off-condition" (Langston *et al.*, 1992)). The patients' disease severity was assessed using the Hoehn & Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS). Twenty-one healthy volunteers, matched for age and gender, were studied as a control group (Table 6.1). Patients with very marked resting tremor were excluded, and in the remaining patients we carefully controlled for tremor influences on the scanning results by recording electromyography (see below).

Subjects were included when they were right-handed (Edinburg Handedness Inventory), had no cognitive dysfunction (i.e. Mini-Mental State Examination > 24, Frontal Assessment Battery > 13), and no vestibular, orthopaedic, neurological or psychiatric diseases. Written informed consent was obtained from all subjects prior to the start of the experiment according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands).

Quantitative gait characteristics were assessed in all subjects. In most subjects this gait assessment could not be performed on the same day as the fMRI experiment (18 patients, 11 controls). The two experiments were performed on average 3.8 days apart (range: 0 – 47 days). To ensure that

patients were in a similar OFF state on both days, the experiments were always performed in the morning, and the UPDRS was assessed on both days (fMRI day: 31.0 ± 11.9; Gait day: 30.6 ± 11.8; p = 0.565).

Table 6.1. Clinical characteristics

Subject	Sex	Age (years)	Disease duration (years)	H&Y	UPDRS III	MMSE	FAB
1	M	52	18	2	49	30	18
2	M	65	14	2.5	35	30	17
3	M	70	15	2.5	35	27	16
4	F	62	6	2	32	29	16
5	F	44	8	2	26	30	18
6	M	69	11	2.5	50	30	17
7	F	54	9	2	38	30	18
8	M	67	6	2	24	29	15
9	M	67	5	2	47	28	17
10	M	42	5	2	31	30	17
11	F	67	3	2	14	30	16
12	M	46	2	2	22	29	18
13	M	49	16	2.5	41	28	14
14	F	54	6	2	20	30	18
15	M	61	9	2	28	24	17
16	F	68	5	2	9	29	18
17	F	60	3	2.5	18	29	18
18	M	65	9	2	26	30	17
19	M	52	15	3	44	28	15
Patients	12 M, 7 F	58.6 ± 9.2	8.7 ± 4.9	2.2 ± 0.3	31.0 ± 11.9	28.9 ± 1.5	16.8 ± 1.2
Controls	12 M, 9 F	57.0 ± 8.8				29.4 ± 0.7	17.7 ± 0.7
P-value		0.571				0.213	0.016

Data represent mean ± sd. H&Y = Hoehn and Yarh Rating Scale; UPDRS III = Unified Parkinson's Disease Rating Scale part 3; MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; M = Male; F = Female

Gait assessment

Gait characteristics were measured with an electronic and pressure-sensitive walkway system (GAITRite, CIR Systems Inc, Clifton, NJ, USA). This system consists of a 4.6 m long walkway, containing six sensor pads encapsulated in a roll up carpet to produce an active area 61 cm wide and 366 cm long. As the patient ambulates across the walkway, the system captures the geometry and the relative arrangement of each footfall as a function of time. The pad controllers on the walkway were covered to prevent visual cues. Subjects were asked to walk over the walkway at their normal and self-preferred speed. This procedure was repeated three times. Given that gait hypokinesia in PD has been linked to an inability to internally generate sufficiently large steps (Morris *et al.*, 1994), we were specifically interested in changes in step length and gait velocity in PD as compared to controls (for details on calculation of these parameters see www.gaitrite.com). We compared normalized step length (step length/leg length) and normalized gait velocity (velocity/leg length) between PD and controls using independent sample t-tests.

Tasks

We used the same protocol that was first validated behaviourally (Bakker *et al.*, 2007a) and then used in a previous fMRI study in young healthy subjects (Bakker *et al.*, 2008). Subjects performed two tasks: motor imagery of gait and a matched visual imagery control task. Both tasks started with the presentation of a photograph showing a corridor with a path in the middle (Fig. 4.1). During the motor imagery task (MI), subjects were asked to imagine walking along this path. During the visual imagery task (VI), subjects were asked to imagine seeing a disc moving along the path. A MI trial started with the presentation of a photograph with a green square as a start marker (Fig. 4.1). Subjects were asked to shortly inspect the picture, close their eyes, imagine walking along the path (starting from the green square and stopping at the green pillar) and finally to open their eyes when they had imagined to have reached the green pillar (see Fig. 4.2 for trial time course). Subjects were instructed to vividly imagine the walking movement, in a first person perspective, as if their legs were moving, but without making any actual movements. A VI trial started with the presentation of a photograph with a black disc as start marker (Fig. 4.1). Subjects were asked to shortly inspect the picture, close their eyes, imagine standing on the left side of the beginning of the path and seeing the disc moving towards the green pillar, and finally to open their eyes when they had imagined the disc reaching the green pillar. During both tasks, the path could have two different widths (narrow, broad). In addition, the green pillar could be placed at five different distances from the green square or the black disc (2, 4, 6, 8, and 10 m). During each trial, subjects signalled that they had started and stopped the imagery by pressing a button. Patients pressed the button with the hand which displayed the least severe tremor (13 left hand, 6 right). Controls were matched to the patients: i.e. 14 controls pressed the button with their left hand and 7 with their right hand. We explicitly instructed subjects not to count during the imagery tasks.

Experimental procedure

During the experiment, subjects were lying supine in the MR scanner. Visual stimuli were presented by means of a PC running Presentation software (Neurobehavioural systems, Albany, USA), and were projected onto a screen at the back of the scanner via a mirror above the subjects' heads. The MI and VI tasks were performed in two successive sessions of 25 minutes each, separated by a break outside the scanner. Task order was counter-balanced across subjects. For each session, the trial order was pseudo-randomized across the experimental factors (i.e. path width (2 levels) and path length (5 levels)). We used two fixed pseudo-randomized orders that were counterbalanced across the two tasks. In between trials a fixation cross was presented (inter-trial interval, ITI: 4-12 sec).

Prior to the first and second block, subjects were given written and verbal instruction about the task they would perform in the next session, followed by a training in the relevant task outside the scanner (15 trials) and inside the MR-scanner (first session only, 7 trials). Prior to the MI task, subjects were asked to walk along short versions (three meters) of both the broad and the narrow paths (3 times for each path width), at a comfortable pace, avoiding to place their feet outside the path. We instructed subjects to pay attention to the feeling of walking along the different path widths, and to imagine walking in a similar way along the two different paths during the imagery trials. To make subjects familiar with the movement of the disc, prior to the VI task, they saw a video of the disc moving through the same corridor as in the photographs. The disc moved for 6 m, in a straight line, at a uniform speed of about 0.8 m/s. We instructed subjects to imagine seeing the disc moving in a similar way along the two different paths during the imagery trials.

Data collection
Button presses were recorded with an MR-compatible keypad (MRI Devices, Waukesha, WI) positioned on the subjects' abdomen.

MR images were acquired on a Siemens 3T Trio system (Siemens, Erlangen, Germany), using an 8 channel head coil for radio-frequency transmission and signal reception. Blood oxygenation level-dependent (BOLD) sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE = 2380 ms/30 ms; 50 ms gap between successive volumes; 35 transversal slices; ascending acquisition; voxel size 3.5 x 3.5 x 3 mm; FOV = 224 mm). High-resolution anatomical images were acquired using an MP-RAGE sequence (TR/TE = 2300/2.92 ms, 192 sagittal slices, voxel size 1.0 x 1.0 x 1.0 mm, FOV = 256 mm).

A concern that arises when comparing cerebral activity during motor imagery of gait in PD patients versus healthy controls is that differences in actual movements (related to parkinsonian tremor or to overt leg movements during motor imagery of gait) might result in changes in cerebral activity between patients and controls. To control for these factors, muscle activity from the forearm and the lower leg was measured during the fMRI experiment. Muscle activity was recorded with an MR compatible EMG (electromyography) system (Brain Products GmBH, Gilching, Germany). Silver/silver-chloride electrodes were placed three cm apart on the tibialis anterior and extensor carpi radialis in a belly tendon montage. Ground electrodes were placed on the lateral malleolus and on the head of the radius. For patients this was done at the side which displayed the most severe tremor (13 right, 6 left). The side of recording in control subjects was matched to the patients (14 right, 7 left).

Finally, eye movements were measured with a video-based infrared eyetracker (Sensomotoric Instruments, Berlin, Germany). These measures allowed us to have online visual inspection of task performance.

Behavioural analysis
For each trial, imagery time (IT) was defined as the time between the button presses indicating the onset and offset of imagery. Trials where subjects failed to press the button (either at the onset or offset of the imagery phase) were excluded from analysis of the imagery-related effects (patients mean [range]: 1.2 [0 to 5] trials; controls: 1.0 [0 to 7] trials). Afterwards, the standard deviation of the mean picture inspection duration and IT was computed and all trials with an average duration of > or < than the mean ± 3 SD were excluded to remove outliers (patients: 1.8 [0 to 5] trials; controls: 1.6 [0 to 2] trials).

We considered the effect of GROUP (PD, controls), TASK (MI, VI), PATH WIDTH (narrow, broad) and PATH LENGTH (2,4,6,8,10 m) on ITs. The significance of the experimental factors was tested within the framework of the General Linear Model using a 2x2x2x5 repeated measures ANOVA. When interactions were significant, the simple main effects were investigated by additional repeated measures ANOVA's. In addition, separate 2x2x5 repeated measures ANOVA's were performed to examine the effects of TASK, PATH WIDTH and PATH LENGTH for each group separately. The alpha-level of all behavioural analyses was set at $p<0.05$, univariate approach. Greenhouse-Geisser corrections were applied whenever the assumption of sphericity was not met, resulting in adjusted P-values based on adjusted degrees of freedom. Finally, we examined with linear regression analysis the relationship between individual ITs and a) individual normalized step length, b) individual normalized velocity.

EMG analysis
Offline MR artefact correction followed the method described earlier (Allen *et al.*, 2000; van Duinen *et al.*, 2005), including low-pass filtering (400 Hz), and down-sampling (1000 Hz). Subsequently, we applied high-pass filtering (25 Hz, to remove possible movement artefacts) and rectification.

We used the EMG recordings from the leg muscle to control for overt leg muscle movements. We considered the root mean square (rms) of the EMG signals measured during the IT (imagery epoch) and during the ITI (inter trial epoch) for each trial of the imagery experiment. For each subject, the average rms value of the EMG measured during the IT epoch was normalized to the average rms value of the ITI epoch, testing for an effect of GROUP (PD, controls) and TASK (MI, VI) with a repeated measures ANOVA.

We used the EMG recording of the forearm muscle to correct for tremor related cerebral activity in the fMRI data. First, the whole EMG time series was segmented (one segment for each EPI volume). Subsequently a time frequency analysis was performed. That is, we calculated (for each segment) EMG power between 0 – 20 Hz. The peak frequency between 4 and 6 Hz. (i.e. the frequency corresponding to the rest tremor) was determined for each individual subject after visual inspection of the average power spectrum. Subsequently, the EMG power at this frequency was extracted in Matlab (MathWorks, Natick, MA) using the FieldTrip toolbox for EEG/MEG analysis (www.ru.nl/neuroimaging/fieldtrip). We also calculated the EMG amplitude and we log-transformed the EMG power to get rid of outliers, leading to 3 tremor-related EMG regressors (power, amplitude and log of power). Last, we applied a z-transformation to each of these three regressors and convolved them with the hemodynamic response function (hrf), before adding them to our statistical model.

Preprocessing of imaging data
Functional data were pre-processed and analyzed with SPM5 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first four volumes of each patient's data set were discarded to allow for T1 equilibration. The remaining functional volumes were spatially realigned using a least squares approach and a 6 parameter (rigid body) spatial transformation (Friston *et al.*, 1995b). Subsequently, the time-series for each voxel was temporally realigned to the acquisition of the first slice. Images were normalized to a standard EPI template centered in MNI (Montreal Neurological Institute) space (Ashburner and Friston, 1997) and resampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 10 mm full-width-at-half-maximum Gaussian kernel.

Anatomical images were spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997), spatially normalized by using the same transformation matrix applied to the functional images and finally segmented into grey matter, white matter, CSF and other nonbrain partitions (Ashburner and Friston, 2005).

Statistical analysis of imaging data – first level
The ensuing pre-processed fMRI time series were analyzed on a subject-by-subject basis using an event-related approach in the context of the General Linear Model (Friston *et al.*, 1995a). The model was aimed at finding regions in which the cerebral response changed as a function of TASK (MI, VI). Also PATH WIDTH and PATH LENGTH were incorporated, which gave rise to a model with twenty different regressors of interest. The model also included separate regressors of no interest, modelling picture inspection, button presses and incorrect trials separately for each session. Each effect was modelled on a trial by trial basis as a concatenation of square-wave func-

tions convolved with a canonical haemodynamic response function, down sampled at each scan, generating a total of 26 task-related regressors (Friston *et al.*, 1998). For the regressors of interest, onsets of the square-wave functions were time-locked to the button press marking the onset of imagery, and durations corresponded to the mean IT across all imagery trials of the subject. For the picture inspection regressors, onsets were time locked to the onset of picture presentation, and offsets were time-locked to the button press marking the onset of imagery. For the button press regressor, onsets were time locked to the button press marking the offset of imagery, and duration was set to zero. For the incorrect trials regressor, onsets were time locked to the onset of picture presentation, and offsets were time-locked to the button press marking the offset of imagery. The potential confounding effects of residual head movement-related effects were modelled using the time series of the estimated head movements during scanning. We included both the original time series, the squared, the first-order derivatives of the originals and the first-order derivatives of the squared (Lund *et al.*, 2005). The intensity changes attributable to the tremor-related movements through the magnetic field were accounted for by using the time series of the mean signal from the white matter, cerebral spinal fluid and out of brain voxels (Verhagen *et al.*, 2006). Finally, the three EMG regressors described above (power, amplitude and log transformation of the power) were modelled, and the data was high-pass filtered (cutoff 128 s) to remove low-frequency confounds such as scanner drifts.

Statistical analysis of imaging data – second level

We report the results of a random effects analysis. The statistical significance of the estimated evoked haemodynamic response was assessed using t-statistics in the context of the General Linear Model. For each subject four contrast images (controls: cMI-broad, cMI-narrow, cVI-broad and cVI-narrow; patients: pMI-broad, pMI-narrow, pVI-broad and pVI-narrow) were calculated and entered into a second level random effects analysis.

Given previous reports on the cerebral correlates of motor imagery of gait, as evoked by this task (Bakker *et al.*, 2008), here we focus on between-groups differences evoked during motor imagery performance. Namely, we were interested in those regions that specifically increased their activity as a function of task in one group, but not in the other group. One way to fulfil these constraints while maintaining sensitivity is to mask the simple main effect (for instance, (pMI > pVI)) with the relative interaction [i.e. (pMI>pVI) > (cMI>cVI); see also (Ramnani *et al.*, 2001)]). In other words, when testing for the differential cerebral activity in patients between the two tasks, we confined our search to regions showing a corresponding TASK*GROUP interaction [(pMI>pVI) > (cMI>cVI); (pVI>pMI) > (cVI>cMI)], using inclusive masking ($p = 0.05$). An equivalent procedure was used to asses the effects of task in controls.

Statistical inference was performed at the voxel level, correcting for multiple comparisons over the search volume (i.e. the whole brain) using false discovery rate (FDR) correction ($p<0.05$). A cluster extend threshold of 10 voxels was used in all comparisons.

Region of interest analysis

We performed a region of interest (ROI) analysis on the MLR. We used the anatomically defined coordinates of the pedunculopontine nucleus (PPN) (Zrinzo *et al.*, 2008) to define the MLR as a region of interest (right and left PPN [6, -26, -13] and [-6, -26, -13] (MNI coordinates)). More specifically, we drew two spherical ROIs centred at these coordinates with a radius of 6 mm. We also performed ROI analyses on those regions that were identified to be involved in motor imagery of gait in our previous study on healthy subjects (Bakker *et al.*, 2008), but that did not show any differential activity between PD patients and controls in the whole brain analysis. These areas involved the right dorsal premotor area [16 -12 74], the right anterior cingulate gyrus [6 0 46], and the left

putamen [-24 -4 8]. We drew spherical ROI's centered at these coordinates with a radius of 10 mm. Within all these ROIs, statistical inference was performed as described above.

Anatomical inference
Anatomical details of significant signal changes were obtained by superimposing the SPMs on the anatomical sections of a representative subject of the MNI series. The atlas of Duvernoy *et al.* (1991) was used to identify relevant anatomical landmarks. The SPM Anatomy Toolbox was used for regions where cytoarchitectonic maps were available (Eickhoff *et al.*, 2005; Scheperjans *et al.*, 2008). The nomenclature of anatomical structures within the cerebellum follows Schmahmann *et al.* (1999). The functional labelling of premotor cortical areas was based on (Mayka *et al.*, 2006; Picard and Strick, 2001).

Brain-behaviour relationship
Finally, we examined whether there was a relationship between changes in cerebral activity during MI relative to VI and a) changes in task performance during MI relative to VI and b) individual gait characteristics. We hypothesized that changes in MI-related cerebral activity in PD might be related to differences in MI-related task performance or to the severity of the gait problems. Therefore, we tested whether individual MI-related cerebral effects (differences in beta-values between MI and VI as indexed by the peak coordinates of the regions that were more active during MI than during VI) correlated with a) behavioural imagery performance (imagery time MI – imagery time VI), and b) individual normalized step length (step length/leg length). Subject-specific beta values were extracted using MarsBar (Brett *et al.*, 2002), and multiple linear regression was used to test these correlations for significance.

Results

Gait characteristics
Patients had a smaller step length than controls (patients 68 ± 7 cm, controls 76 ± 10 cm, $p=0.01$), and also tended to walk slower (patients 127 ± 16 cm/s, controls 140 ± 20 cm/s, $p=0.06$ (statistics on normalized data)). These findings indicate that gait was mildly impaired in PD patients.

Behavioural results
Imagery times were not different between patients and controls (GROUP: $F(1,38) = 2.0$, $p = 0.163$). The effect of task on imagery times did not differ significantly between the two groups, although PD patients tended to be slower for MI (as compared to VI) than controls (TASK*GROUP interaction: $F(1,38) = 3.1$, $p = 0.088$) (Fig. 6.1A). Imagery times increased with increasing path length in both tasks, and this effect was not different for patients and controls (main effect of PATH LENGTH: $F(1.1,40.9) = 136.7$, $p < 0.001$; GROUP*PATH LENGTH: $F(1.1,40.9) = 0.6$, $p = 0.451$) (Fig. 6.1B). Crucially, the effect of path width on imagery times differed for the different tasks (TASK*PATH WIDTH interaction: $F(1,38) = 16.6$, $p < 0.001$). A smaller path width resulted in longer imagery times in the MI task ($F(1,38) = 17.7$, $p < 0.001$), but had no effect on imagery times in the VI task ($F(1,38) = 0.6$, $p = 0.452$). This differential effect of path width was the same for patients and controls (GROUP*TASK*PATH WIDTH: $F(1,38) = 0.4$, $p = 0.535$) (Fig. 6.1C), indicating that in both groups, motor imagery was sensitive to the environmental constraints imposed by a narrow walking path that allows only for positioning one foot at a time on the path. This finding suggests that both groups solved the MI task by using kinaesthetic motor imagery.

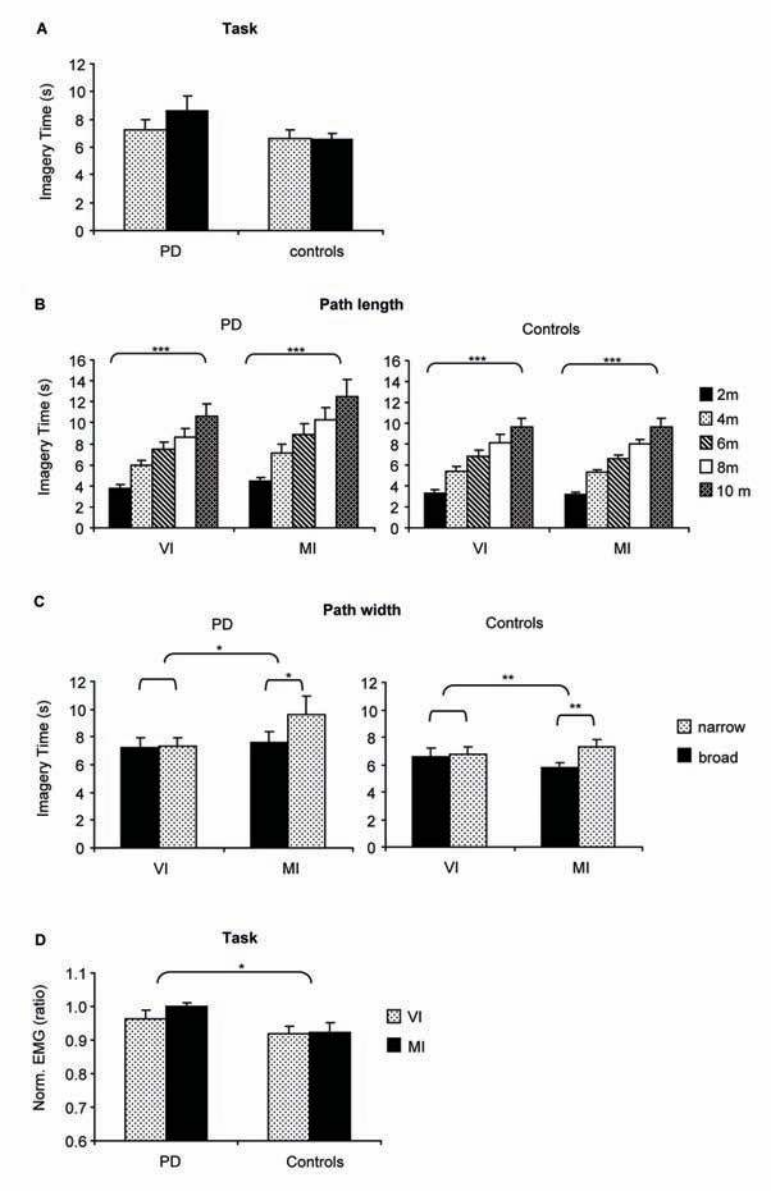

Figure 6.1. Behavioural results. *Imagery times are shown for both patients (PD) and controls, separately for;* ***A)*** *each task [motor imagery (MI), visual imagery (VI)],* ***B)*** *the five different path lengths [2, 4, 6, 8, and 10 m] and* ***C)*** *the two different path widths [broad, narrow].* ***D)*** *Averaged normalized electromyography (Norm. EMG) values measured during MI and VI trials, normalized to average ITI EMG values on a subject by subject basis. Data represent mean ± SEM. ***P < 0.001, **P < 0.01, *P < 0.05.*

Relationship between behavioural results and gait characteristics

We examined the relationship between motor imagery performance and actual gait characteristics. There was no significant relationship between individual motor imagery time and individual normalized step length (patients: $r = 0.2$, $p = 0.332$; controls: $r = 0.1$, $p = 0.593$), and no relationship between individual motor imagery time and individual normalized velocity (patients: $r = 0.1$, $p = 0.721$; controls: $r = 0.3$, $p = 0.207$). This finding is at odds with previous studies showing a close temporal relationship between actual and imagined movements (for example Sirigu *et al.*, 1996; Stevens, 2005). However, in those studies both imagined and actual movements were performed in the same environment and in close temporal proximity. In contrast, in this study imagined and actual gait movements were performed in different days, in different laboratories, using different visual input (i.e., during motor imagery of gait, subjects had to estimate the distance to be walked from a 2-D photograph, see Fig. 4.1).

Electromyography

We found no differences in EMG activity between VI and MI (TASK: $F(1,38) = 0.9$, $p = 0.341$). We did observe a significant difference in EMG activity between patients and controls (GROUP: $F(1,38) = 5.3$, $p = 0.026$). Inspection of Figure 6.1D clearly indicates that control subjects moved more during the inter-trial interval than during the imagery trials, whereas patients moved equally much in both. Crucially, this effect of group was not different for the different tasks (TASK*GROUP interaction $F(1,38) = 0.7$, $p = 0.418$), indicating that the VI task adequately controlled for this difference between the two groups. Accordingly, we focus this report on the between-groups differences evoked during motor imagery as compared to visual imagery trials.

Differential cerebral activity during motor imagery of gait across groups

Relative decreases in cerebral activity in PD patients

When searching over the whole brain, PD patients showed a decrease in differential motor imagery-related activity (MI>VI) compared to controls along the border between the dorsal precentral sulcus and the superior frontal gyrus, bilaterally (53.7 % fell within left BA 6, 37.5 % within right BA 6) (Fig. 6.2A; Table 6.2). The local maximum of this cluster was functionally defined as the supplementary motor areas (SMA), following the maps of (Mayka *et al.*, 2006; Picard and Strick, 2001). Furthermore, PD patients showed a significant decrease in differential activity between MI and VI in the right and left superior parietal lobule (SPL) (Fig. 6.2B; Table 6.2). Both parietal clusters fell within area 5L (55% of right cluster, 96.3% of left cluster), furthermore 29% of the right cluster fell within area 5M (Scheperjans *et al.*, 2008). Finally, PD patients showed a significant decrease in differential activity between MI and VI in lobules III and IV of Larsell in the cerebellum (Fig. 6.2C; Table 6.2). No areas were found that were less active during VI than during MI in patients relative to controls.

When restricting the search of relative decreases in cerebral activity within the a priori ROIs centred on the right dorsal premotor cortex, right anterior cingulate, left putamen and MLR, we found no additional decreases in cerebral activity between PD patients and controls.

Table 6.2. Stereotactic coordinates of the local maxima

Contrast	Functional mask	Search volume	Anatomical label	Functional label	Hemi-sphere	t-value	p-value	x	y	z
cMI>cVI	cMI>cVI > pMI>pVI	Whole brain	Superior frontal gyrus	SMA		5.09	0.009	0	-14	70
			Superior frontal gyrus	SMA	L	4.95	0.009	-8	-20	72
			Paracentral lobule	SMA	R	3.85	0.027	6	-26	74
			Superior parietal lobule	Area 5L	R	4.83	0.009	10	-52	66
			Superior parietal lobule	Area 5L	L	4.20	0.015	-16	-46	70
			Cerebellum	Lobule IV	R	4.02	0.019	24	-34	-36
			Cerebellum	Lobule III – IV	L	3.84	0.027	-18	-34	-40
pMI>pVI	pMI>pVI > cMI>cVI	VOI [6 -26 -12]	Posterior mid-mesencephalon	Mesencephalic locomotor region	R	3.40	0.010	2	-30	-12
		VOI [-6 -26 -12]	Posterior mid-mesencephalon	Mesencephalic locomotor region	L	3.39	0.010	-2	-30	-12

Results are corrected for multiple comparisons (FDR, p<0.05). Stereotactic coordinates are reported in Montreal Neurological Institute (MNI) space. Details on the anatomical and functional labeling can be found in the Methods and Results sections. c = controls; L = left; MI = motor imagery; p = PD patients; R = right; SMA = supplementary motor area; VI = visual imagery; VOI = volume of interest (radius:6 mm).

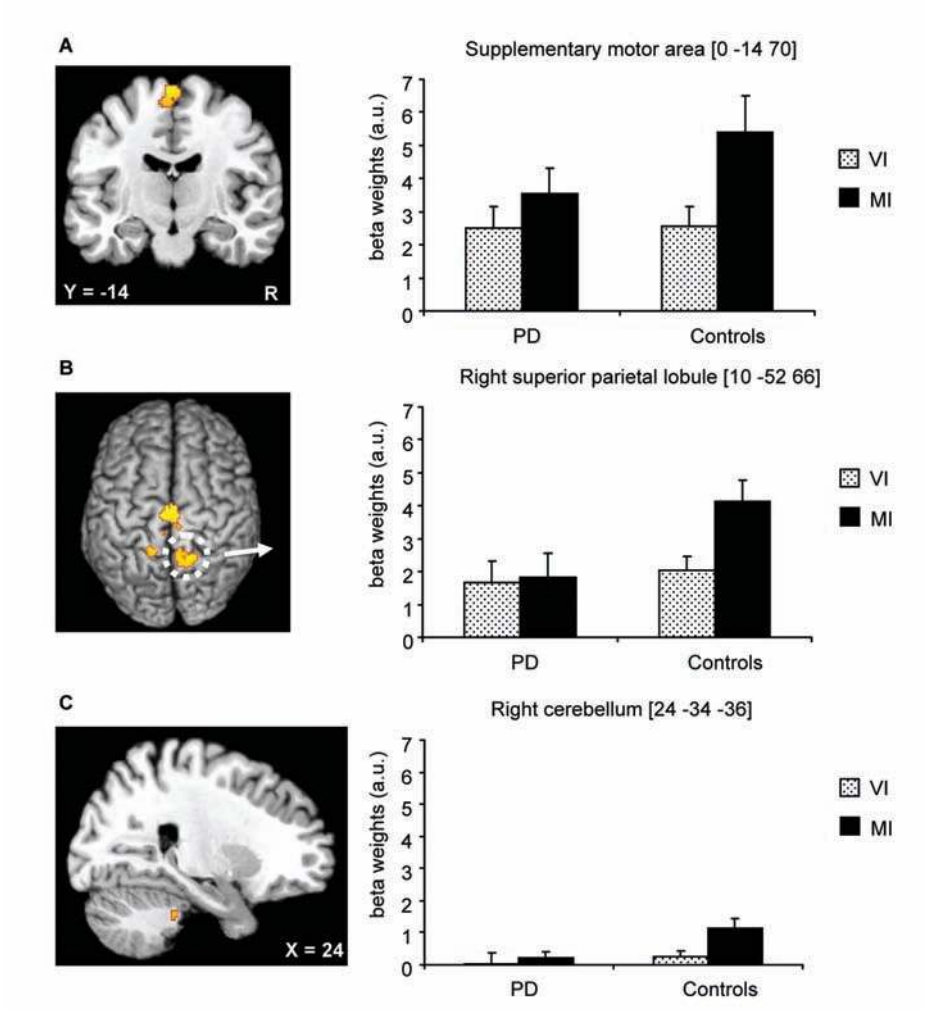

Figure 6.2. Brain areas in which the relative increase in activity for motor imagery (MI) versus visual imagery (VI) was greater in controls than in PD patients*. On the left, statistical parametric maps (SPM) of increased activity in supplementary motor area (left, middle), superior parietal lobule (middle, right) and cerebellum [corrected for multiple comparisons (p < 0.05) using FDR], superimposed on* ***A)*** *a coronal brain section,* ***B)*** *a rendered brain viewed from the top, and* ***C)*** *a sagittal brain section. On the right, beta weights (mean ± SEM) of the local maximum from A) supplementary motor area (SMA), B) right superior parietal lobule (SPL), and C) right cerebellum during MI and VI in patients and controls.*

Relative increases in cerebral activity in PD patients

When searching over the whole brain, there were no supra-threshold differential patterns of imagery-related activity (MI > VI) that were stronger in patients relative to controls. However, when restricting the search of this effect to the a priori ROIs (see above), there were two significant clusters in the right and left MLR that showed an increase in differential activity between MI and VI (MI>VI) in PD compared to controls (Fig. 6.3; Table 6.2). No areas were found that were more active during VI than during MI in patients relative to controls.

Brain-behaviour relationship

The change in cerebral activity during MI relative to VI in the SMA correlated positively and significantly with normalized step length in the patient group (i.e. patients with a smaller step length displayed less differential activation of MI relative to VI). In the SPL this positive correlation tended to be present in the control group (Fig 6.4; Table 6.3). In the other activated regions we found no correlations between normalized step length and changes in cerebral activity. The change in cerebral activity during MI relative to VI in the right cerebellum correlated positively and significantly with imagery time in the control group (i.e. controls with a greater increase in imagery time during MI relative to VI displayed increased differential activation of MI relative to VI). These correlations should be interpreted with caution given that they are at the border of significance and we did not correct for multiple comparisons.

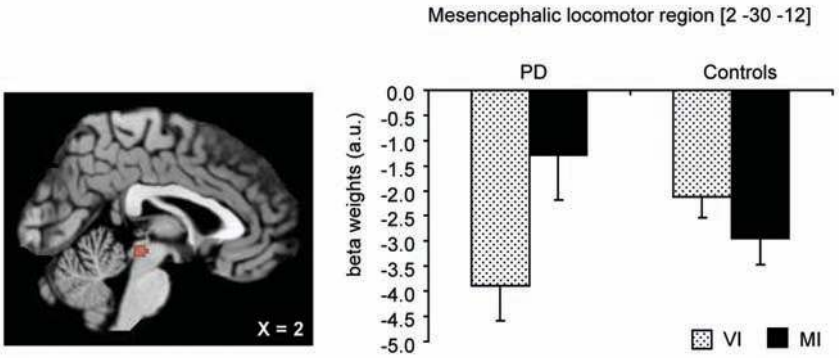

Figure 6.3 Relative increase of activity during MI versus VI in the mesencephalic locomotor region (MLR), greater for PD patients than for controls, identified after a region of interest analysis. *Statistical parameter map (SPM) of increased activity in the mesencephalic locomotor region [thresholded at p < 0.001 (uncorrected) for display purposes], superimposed on a coronal brain section (left). Beta weights (mean ± SEM) during MI and VI in patients and controls (right).*

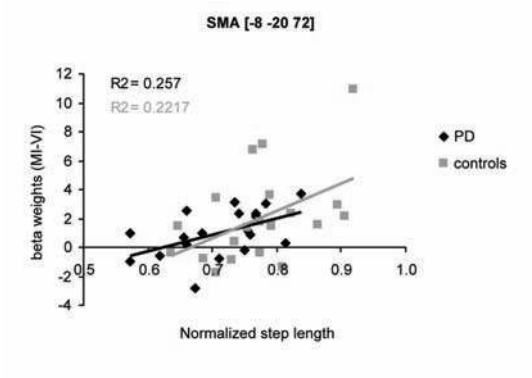

Figure 6.4. Brain-behaviour relationship. *Difference in beta weights between MI and VI (MI-VI) in the supplementary motor area (SMA) across subjects as a function of normalized step length for controls (grey squares) and PD patients (black diamonds).*

Table 6.3. Brain-behaviour relationship

		Normalized step length		Imagery time (MI-VI)	
Region	**Group**	**Standardized coefiicient beta**	**P-value**	**Standardized coefiicient beta**	**P-value**
SMA [0 -14 70]	PD patients	0.401	0.081	0.291	0.196
	Controls	0.264	0.243	0.323	0.157
SMA [-8 -20 72]	PD patients	0.468	0.046*	0.176	0.429
	Controls	0.340	0.105	0.395	0.064
SMA [6 -26 74]	PD patients	0.397	0.114	-0.085	0.726
	Controls	0.235	0.319	0.247	0.296
SPL [10 -52 66]	PD patients	0.295	0.227	0.225	0.353
	Controls	0.399	0.054	0.375	0.068
SPL [-16 -46 70]	PD patients	0.099	0.697	0.201	0.433
	Controls	0.083	0.725	0.335	0.166
Cerebellum [24 -34 -36]	PD patients	-0.028	0.913	0.199	0.443
	Controls	-0.387	0.088	0.484	0.037*
Cerebellum [-18 -34 -40]	PD patients	0.192	0.451	0.127	0.616
	Controls	-0.139	0.572	0.255	0.306
MLR [-2 -30 -12]	PD patients	-0.177	0.474	0.348	0.169
	Controls	-0.168	0.497	-0.117	0.635

*SMA = supplementary motor area; SPL = superior parietal lobule; MI = motor imagery, VI = visual imagery; *P<0.05*

Discussion

In this study, motor imagery was used as a tool to investigate alterations in neural activity related to planning of gait in Parkinson's disease. Behaviourally, patients had a smaller step length during actual walking. During motor imagery of gait, performance was comparable between PD patients and controls. Cerebrally, the PD patients showed a relative decrease in motor imagery activity in

the bilateral SMA, SPL, and cerebellar lobule IV, and a relative increase in the MLR. Furthermore, activity in the SMA was positively correlated with step length, as measured during actual gait performance. These alterations of the motor system of PD patients during imagery of gait were independent from changes in motor execution, somatosensory processing, or task difficulty.

Behavioural performance

In functional neuroimaging studies it is important to sample cerebral activity during tasks that patients can perform effectively (Price and Friston, 1999). Accordingly, we selected patients with relatively mild gait problems (step length: patients 68 ± 7 cm, controls 76 ± 10 cm). Imagery times were recorded on a trial by trial basis, in order to quantify task performance. Patients performed the task proficiently, such that there were no overall differences in imagery times between PD and controls, and in both groups imagery times were equally sensitive to both the length and the width of the path. These findings indicate that PD and control groups were equally effective in solving the motor imagery task, and confirm the ability of this motor imagery procedure to evoke kinestethic imagery (Bakker *et al.*, 2007a; Bakker *et al.*, 2008; Stevens, 2005). Crucially, these results also exclude that between-group cerebral differences during motor imagery performance could be accounted for by differences in task difficulty.

Cerebral control of gait imagery in PD

PD patients showed a relative decrease in activity in the bilateral SMA, SPL, and cerebellar lobule IV during motor imagery of gait. These data are consistent with a study showing reduced cerebral activity in the left medial frontal area, the right precuneus, and the left cerebellar hemisphere in PD patients after physical gait performance on a treadmill (Hanakawa *et al.*, 1999b). Having examined motor imagery of gait instead of actual gait performance, here we can show that these changes in cerebral activity are specifically related to organizing the gait plan, rather than a by-product of altered motor execution or somatosensory processing. Furthermore, a novel finding of our study is that PD patients showed a relative increase of activity in the MLR during motor imagery of gait (the possible implications of this will be discussed later). Finally, changes in cerebral activity could be localized in more detail compared to previous work. For example, the effect in the cerebellum was spatially specific, located close (7 mm) to portions of the cerebellum previously associated with tactile stimulation of the feet (Bushara *et al.*, 2001), and with performance of actual foot movements (Dimitrova *et al.*, 2006).

Supplementary motor area

It has been proposed that underactivity in mesial motor areas underlies hypokinesia in PD. For example, neuroimaging studies showed under-activation of the SMA when hypokinetic PD patients perform sequential and bimanual movements (Sabatini *et al.*, 2000; Samuel *et al.*, 1997), single joystick movements (Haslinger *et al.*, 2001), or motor imagery of joystick movements (Samuel *et al.*, 2001). Although hypokinetic gait has been linked to an inability to internally generate sufficiently large steps (Morris *et al.*, 1994), only limited evidence is available regarding the involvement of mesial motor areas in hypokinesia of lower limb movements. Patients with SMA lesions can develop a hypokinetic gait pattern (Chung *et al.*, 2004), and bilateral motor cortex stimulation in a patient with levodopa-resistant akinesia results in increased step size and increased activity in the left SMA (Tani *et al.*, 2007). Furthermore, an electrophysiological index preceding gait initiation and with a mesial-frontal origin (the Bereitschaftspotential, (Deecke and Kornhuber, 1978)) was reduced in PD patients (Vidailhet *et al.*, 1993). Finally, it has been suggested that gait hypokinesia in PD might be caused by a mismatch between the cortically selected step size and that maintained by the basal ganglia (Morris *et al.*, 2005). Our finding of reduced SMA activity in PD patients during motor imagery of gait further qualifies those findings, showing that patients with weaker SMA activity

during motor imagery of gait had a proportionally smaller step length during actual walking. We infer that the reduced SMA activity during motor imagery of gait might be related to difficulties with the planning of an appropriate step length in PD.

Superior parietal lobule & cerebellum

During motor imagery of gait, cerebral activity in the SPL and in the cerebellum was reduced in PD patients compared to matched controls. This result confirms previous SPECT findings related to the execution of gait movements in PD patients (Hanakawa *et al.*, 1999b). The SPL is involved in integrating visual and somatosensory information into the appropriate motor coordinates required for making spatially directed movements (Andersen, 1997; Wenderoth *et al.*, 2006). The imagery-related effects we observe cannot be related to altered processing of proprioceptive feedback. Rather, the reduced activity in the SPL and cerebellum is likely related to alterations in generating predictions of the sensory consequences of the imagined movements. Both actual and imagined movements involve the generation of predictions on the sensory consequences of the action (Blakemore and Sirigu, 2003). During movement execution, the predicted sensory consequences are compared to the actual sensory feedback. During motor imagery, sensory predictions are generated in the absence of concurrent action production. The parietal lobe is thought to be involved in generating these sensory predictions (Blakemore and Sirigu, 2003; Wolpert *et al.*, 1998). In addition, the cerebellum is thought to operate together with the SPL in comparing predicted and actual sensory consequences of a movement (Blakemore and Sirigu, 2003; Miall *et al.*, 2007). Accordingly, the reduced SPL and cerebellar activity observed in PD patients during motor imagery of gait might reflect disturbances in predicting the sensory consequences of the motor plan. These disturbances may arise as a result of progressive impairments in processing afferent proprioceptive input (Maschke *et al.*, 2003) and integrating this input with motor plans in PD patients (Lewis and Byblow, 2002; Rickards and Cody, 1997; Keijsers *et al.*, 2005; Almeida *et al.*, 2005).

Mesencephalic locomotor region

The role of the MLR in gait disturbances in PD is actively debated (for reviews see Pahapill and Lozano, 2000; Winn, 2006), mainly with evidence from animal studies. For example, lesions or high-frequency stimulation in the PPN result in akinesia and gait problems in monkeys (Kojima *et al.*, 1997; Munro-Davies *et al.*, 1999; Nandi *et al.*, 2002b), whereas low-frequency stimulation or disinhibition of the PPN can alleviate akinesia in MPTP monkeys (Jenkinson *et al.*, 2006; Nandi *et al.*, 2002a). In humans, lesions in the PPN also result in gait problems (Kuo *et al.*, 2008; Masdeu *et al.*, 1994), and recent reports suggest that low-frequency deep brain stimulation of the PPN improves gait problems in PD patients that are otherwise largely resistant to treatment (Mazzone *et al.*, 2005; Plaha and Gill, 2005; Stefani *et al.*, 2007). Furthermore, the neuronal degeneration occurring in the PPN of PD patients is correlated to the severity of their symptoms (Zweig *et al.*, 1989). Accordingly, it has been suggested that changes in neuronal activity in the MLR could account for gait problems in PD (Pahapill and Lozano, 2000).

Several different processes might underlie changes in neuronal activity in the PPN in PD. Firstly there is the loss of (mainly cholinergic) neurons from the PPN (Hirsch *et al.*, 1987; Zweig *et al.*, 1989). Secondly, due to basal ganglia alterations, the PPN of PD patients receives increased excitatory input from the subthalamic nucleus (STN), and increased inhibitory input from the globus pallidus interna (GPi) and substantia nigra pars reticularis (SNr) (Mena-Segovia *et al.*, 2004). Accordingly, the loss of cholinergic neurons, together with the changes in the balance between the STN and GPi/SNr inputs, is likely to determine the alterations in neuronal activity in the PPN in PD. Several studies report increased PPN activity in animal parkinsonian models (Breit *et al.*, 2001; Orieux *et al.*, 2000), yet others report the opposite pattern (Mitchell *et al.*, 1989).

Here we show that imagining to walk evokes relatively stronger MLR responses in PD patients than in matched controls, highlighting the importance of this structure for understanding gait disturbances in PD (Chastan *et al.*, 2009). The current findings suggest that MLR neurons are overactive in PD during gait-related tasks. It has been suggested that a physiological role of overactive PPN neurons in the parkinsonian state could be a compensatory mechanism of the excitatory projections from the PPN to the substantia nigra (Bezard *et al.*, 1997; Bezard and Gross, 1998; Breit *et al.*, 2001). More precisely, increased activity of these excitatory projections to the substantia nigra might increase the activity of the dopaminergic nigrostriatal projections in order to overcome the imbalance induced by the degeneration of dopaminergic nigrostriatal neurons (Futami *et al.*, 1995; Kitai *et al.*, 1999). However, a compensatory role of the MLR might appear counter-intuitive, given that the brainstem is one of the first affected structures in PD (Braak *et al.*, 2002). Furthermore, the relative increase in MLR BOLD signal that we observed in PD patients during motor imagery, occurred in the context of an overall reduction of BOLD signal (as compared to the inter-trial period), and was opposite to the relative decrease in BOLD signal in controls during motor imagery compared to visual imagery. Under the assumption that a reduction in BOLD signal is a marker of neuronal deactivation (Logothetis, 2008; Shmuel *et al.*, 2006), these findings suggest that in controls there is an increased deactivation of the MLR during motor imagery compared to visual imagery, whereas in PD patients there is a reduced deactivation. The opposite effects observed in PD patients and in controls suggest that the increased MLR activity in PD could reflect altered neuronal processing in this structure, and it might in fact be causing the gait problems observed in PD. Further work is necessary to establish whether the altered MLR activity observed in PD patients reflects compensatory or primary disease processes.

Interpretational issues

Although the basal ganglia are affected in PD, and have been shown to be involved in motor imagery of gait (Bakker *et al.*, 2008), cerebral activity in the basal ganglia did not differ between PD patients and controls in the current study. We believe that this is likely to be a false negative, possibly related to MR artefacts due to iron depositions in the basal ganglia. These depositions increase with age, resulting in substantial signal drop in the affected structures (Schenker *et al.*, 1993). We examined elderly subjects, and we found low MR signal in the basal ganglia of several subjects. In addition, it is well-known that striatal dopamine levels decline monotonically with age (Martin *et al.*, 1989), and this may have driven the elderly subjects of our control group to solve the imagery task without relying on the basal ganglia, as young volunteers do (Bakker *et al.*, 2008).

Besides their continuous gait problems, about half of the PD patients tested in this study experienced "freezing of gait". It remains unclear whether similar neural mechanisms underlie the episodic phenomenon of freezing of gait and the continuous hypokinetic gait disorder characteristic of PD (Bartels *et al.*, 2003; Nieuwboer *et al.*, 2007). Accordingly, it is possible that some of the observed changes in cerebral activity may be specifically related to freezing of gait. Unfortunately, the number of freezers and non-freezers was not sufficient to directly compare them in the current study. We are currently investigating this issue in a follow-up study.

Conclusion

Our results show that although behavioural performance was comparable, motor imagery of gait was supported by different cerebral networks in PD compared to controls. In PD, motor imagery of gait was associated with reduced activity bilaterally in the SMA, SPL and cerebellum, and with increased activity in the MLR. We suggest that gait problems in PD might arise from altered voluntary cortical control of movements, as indexed by reduced responses in the fronto-striatal and cerebello-parietal circuits. In addition, our results point to a role of brainstem locomotor centres in

the planning of gait in PD. It remains to be seen whether these centres compensate for or exacerbate gait disturbances in PD.

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Chapter

C7

Summary and outlook

Summary and outlook

The research described in this thesis examined the supraspinal control of gait in both healthy subjects and in patients with Parkinson's disease (PD). More specifically, motor imagery was used to examine the cerebral structures involved in the planning of gait, while avoiding sensory and motor confounds related to motor execution. The thesis started with a discussion of the contribution of functional neuroimaging to the understanding of supraspinal gait control in humans, both in healthy subjects and in patients with PD (*Chapter* 2). A critical discussion was provided highlighting the advantages and disadvantages of the different approaches that have been used to address this issue. Subsequently, a new experimental protocol was described that allows for studying and quantifying motor imagery of gait in a neuroimaging environment (*Chapter* 3). This protocol was used to gain further insight into the cerebral circuitry underlying the planning of gait. First, changes in cerebral activity and corticospinal excitability during motor imagery of normal and precision gait were examined in healthy subjects using fMRI (*Chapter* 4) and TMS (*Chapter* 5) respectively. Afterwards, motor imagery was used to identify those cerebral structures specifically involved in problems with planning of gait in PD patients using fMRI (*Chapter* 6).

Functional neuroimaging of gait

Functional neuroimaging of gait is not straightforward. Several different approaches have been used ranging from the imaging of actual gait performance to the study of initiation and imagery of gait, and each approach has its own advantages and disadvantages (Table 2.1). For example, an advantage of recording cerebral activity during physical gait performance is that cerebral activity is directly related to actual walking. However, disadvantages are that studying a walking person does not allow for discriminating whether the evoked activity is due to sensory input or motor output, and that only a limited number of neuroimaging techniques can be used (because of movement artefacts).

Advantages of recording EEG during gait initiation are that this provides a direct measure of electrophysiological activity in the brain at a high temporal resolution, and that there are only minimal confounds of changes in sensory input. However, disadvantages are that spatial resolution is low and that the approach is challenging due to movement artefacts.

Recording of cerebral activity during motor imagery of gait has practical advantages since it does not involve any actual movements, and subjects can be studied while they remain in a recumbent position. As such, this approach allows for the use of imaging techniques such as fMRI and PET. This is important, since these techniques provide relatively high spatial resolution and whole-brain coverage. Furthermore, a conceptual advantage in using motor imagery is that it allows researchers to examine the planning of movements, while avoiding sensory and motor confounds related to motor execution. This might be particularly useful in patient populations where gait problems seem caused partly by problems with motor planning, such as in PD. However, disadvantages are that evidence for the cerebral overlap between imagery and execution has been mostly obtained from simple finger and hand movements (Lang *et al.*, 1994; Deiber *et al.*, 1998; Porro *et al.*, 1996; Roth *et al.*, 1996; Stephan *et al.*, 1995), whereas only limited evidence is available for gait (Miyai *et al.*, 2001), and that it is difficult to monitor task performance during motor imagery of gait.

Quantifying motor imagery of gait in a neuro-imaging environment

To use motor imagery to its full extent it is important to tackle the problem of quantifying task performance. This is especially important in neuroimaging studies given the importance of sampling cerebral activity during tasks that patients can perform effectively (Price and Friston, 1999). However, differently from the extensive work done on imagery of hand and arm movements

(Decety and Michel, 1989; Helmich *et al.*, 2007; Johnson-Frey, 2004; Parsons, 1987; Parsons, 1994), it remains unclear how to ascertain whether subjects actually perform motor imagery of gait. Accordingly, a quantitative approach to motor imagery of gait was developed, based on mental chronometry (*Chapter* 3).

Mental chronometry refers to inferring the time course of information processing in the nervous system (Donders, 1969). A close temporal correspondence between motor imagery and actual movements would suggest that subjects are able to perform motor imagery accurately. For example, it has been shown that both actual and imagined walking conforms to Fitts' law (Decety, 1991; Decety and Jeannerod, 1995; Stevens, 2005). This law, originally obtained in the context of manual aiming movements (Fitts, 1954), describes the inverse and logarithmic relationship that links the difficulty of a movement and the speed with which the movement can be performed. For example, Stevens *et al.* (2005) showed that both for actual and imagined walking, movement times increase with increasing movement distance (greater path length) and movement difficulty (smaller path width). The effects were specific for motor tasks, given that during a visual imagery control task, movement times were only influenced by movement distance and not by movement difficulty.

For the purpose of this thesis, the set-up of Stevens *et al.* (2005) was adapted to a neuroimaging environment (Figures 4.1 & 4.2). We were able to largely replicate their results showing that it is possible to obtain behavioural indexes that distinguish between motor and visual imagery, and that show the high temporal correspondence between actual and imagined gait (Figure 3.2, 3.3 & 3.4).

The behavioural recordings provided useful information about task performance in this thesis. Imagery times suggested that subjects performed the imagery tasks proficiently in both the fMRI experiments (Figures 4.3 & 6.2) and the TMS experiment (Figure 5.4). Furthermore, it was shown that PD patients and controls were equally sensitive to the constraints associated with imagining to walk on supports of different width and length (Figure 6.2). Finally, trials could be excluded in which subjects were not able to perform the task correctly, as evidenced by extremely large or small imagery times.

It has been argued that any close temporal relationship between actual and imagined movements might be attributable to tacit knowledge about how long it would take to actually execute the movement (Pylyshyn, 2002). This is an inherent problem of all mental chronometry studies. Therefore, before using the new protocol to examine gait problems in PD patients, it was important to make sure that the motor imagery task evoked specific responses within the motor system.

The neural circuit underlying motor imagery of gait in healthy subjects

Cerebral activity

Motor imagery of gait resulted in increased cerebral activity bilaterally in the dorsal premotor cortex, in the superior parietal lobule, in the right rostral cingulated zone posterior, and in the left putamen (Figure 4.4A & Table 4.2). The cerebral responses to motor imagery of gait were contiguous to, but spatially distinct from, regions involved in motor imagery of hand movements (Figure 4.4B). These findings suggest that motor imagery of gait evoked specific responses within the motor system. Another important finding was that the increased spatial accuracy required for imagining walking along a narrow path increased cerebral activity bilaterally in the superior parietal lobule and in the right superior middle occipital gyrus, together with increased effective connectivity between these regions and the dorsal premotor areas controlling foot movements (Figure 4.5 &

Table 4.3). These results emphasize the role of cortical structures outside primary motor regions in imagining locomotion movements when accurate foot positioning and increased postural control is required.

Corticospinal excitability
Imagined foot dorsiflexions increased MEP areas in both a task-related muscle (TA), and a task-unrelated muscle (FDI), with larger increases in the task-related muscle (Figure 5.3). These results show that motor imagery of simple lower limb movements increases corticospinal excitability. Overall, imagined walking did not change MEP areas. However, subjects with larger increases in TA during imagined foot dorsiflexion also showed larger increases in TA during imagined walking (Figure 5.5). This finding suggests that corticospinal effects of a simple imagery task can predict corticospinal effects of a more complex imagery task involving the same muscle. The fact that no overall increase in corticospinal excitability during motor imagery of gait was found might be related to the timing of the TMS pulses. Our motor imagery of gait protocol did not allow for keeping track of the phases of the imagined walking movements. Therefore, the delivery of the TMS pulses was not linked to a particular phase of the gait cycle. Further work should reveal whether corticospinal excitability might only be increased during particular phases of the gait cycle.

The neural circuit underlying motor imagery of gait in Parkinson's disease
The ultimate goal of this thesis was to use motor imagery to gain further insight in the cerebral circuitry underlying problems with the planning of gait in PD (Chapter 6). It was found that in PD, there was a relative decrease in activity in the bilateral supplementary motor area, superior parietal lobule, and cerebellar lobule IV during motor imagery of gait (Figure 6.3), and a relative increase in activity in the mesencephalic locomotor region (Figure 6.4). Furthermore, supplementary motor area activity was positively correlated with step length, as measured during actual walking (Figure 6.5). We infer that the reduced supplementary motor area activity during motor imagery of gait might be related to difficulties with the planning of an appropriate step length in PD. The reduced superior parietal lobule and cerebellar activity might reflect disturbances in predicting the sensory consequences of the motor plan. Further research is necessary to be able to make clear inferences on the increased MLR activity found in this study.

Conclusions
Motor imagery is a useful tool to gain further insight in the cerebral structures involved in gait, but it is important to monitor task performance during the experiment. Our newly developed motor imagery protocol allows for monitoring task performance during motor imagery of gait. Using this protocol it was shown that cortical structures outside primary motor regions are involved in imagining gait movements when accurate foot positioning is required. Furthermore it was shown that although behavioural performance was comparable, motor imagery of gait was supported by different cerebral networks in PD compared to controls. More specifically, gait problems in PD might arise from altered voluntary cortical control of movements, as indexed by reduced responses in the fronto-striatal and cerebello-parietal circuits. In addition, our results point to a role of brainstem locomotor centres in the planning of gait in PD. It remains to be seen whether this role compensates for or exacerbates gait disturbances in PD.

Outlook for future research
Functional neuroimaging studies have given a first insight in the cerebral structures involved in gait control. Up to now most studies (including ours) have been exploratory, examining which cerebral structures are activated during performance of a certain gait-related task. The time seems ripe for assembling these scattered observations into a coherent computational model of gait control in hu-

mans, able to generate testable predictions. Up to now computational models on the neural control of gait have mainly focused on how the central pattern generators coordinate walking movements (Grillner, 2006). It would be useful to start developing computational models that focus on how cortical and subcortical structures are involved in visuomotor control during walking. Such models have already been used to examine the cerebral circuits underlying visuomotor control of arm movements (see for example Ghahramani and Wolpert, 1997; Nakahara *et al.*, 2001). The findings of the studies in this thesis might serve as a basis for developing such computational models.

Further work is needed to develop new quantitative approaches to motor imagery of gait that allow for examining other patient groups and other aspects of gait control. For example, the current protocol was quite complex (involving picture inspection, distance estimation, opening/closing eyes and button presses) and might therefore be too complicated for patients with mild cognitive impairment. Accordingly, development of a simpler protocol for such patients would be useful. Furthermore, the current protocol allowed for examining motor imagery of normal and precision gait, but gait problems in PD become especially pronounced during turning (Huxham *et al.*, 2008; Stack and Ashburn, 2008; Visser *et al.*, 2007) and external cues have been shown to improve gait problems in PD (Keus *et al.*, 2007; Nieuwboer *et al.*, 2007). Therefore, it would be interesting to develop quantitative approaches for motor imagery of turning or motor imagery of walking with external cues.

In this thesis we have identified several cerebral structures showing altered activity in PD patients during motor imagery of gait, suggesting that these regions might be involved in the problems with planning of gait in PD. Further research should reveal whether normalizing cerebral activity in those structures can improve gait performance in PD. For example, we found reduced activity in the SMA. Neural activity in the SMA might be modified using rTMS or intracranial electrical stimulation. It has been shown that motor cortex stimulation improves gait in a patient with levodopa-resistant akinesia (Tani *et al.*, 2007). Furthermore, motor cortex stimulation was accompanied by an increase in cerebral activity in the SMA, suggesting that gait may have been improved by an improved functioning of the SMA. In PD, gait improves after combined motor cortex and dorsolateral prefrontal cortex rTMS (Lomarev *et al.*, 2006). However, to our knowledge no study has specifically examined the effects of motor cortex or SMA stimulation on gait performance in PD.

We also found increased cerebral activity in the MLR in PD. There is increasing evidence that deep brain stimulation in this region can improve gait problems in PD (Mazzone *et al.*, 2005; Plaha and Gill, 2005; Stefani *et al.*, 2007). However, the exact mechanisms underlying these gait improvements remain largely unclear. Gait improves best when the PPN is stimulated at relatively low frequencies, around 25 Hz (Stefani *et al.*, 2007). This is much slower compared to the very high-frequency stimulation (130-185 Hz) used to block neural overactivity in the subthalamic nucleus or globus pallidus (Stefani *et al.*, 2007). Accordingly, low frequency PPN may stimulate neural activity, rather than blocking it. However, it remains unclear whether cerebral activity in the PPN is intrinsically increased or reduced in PD. Animal models in PD remain inconclusive about alterations in neural activity in the PPN in PD: there are several studies reporting increased PPN activity (Breit *et al.*, 2001; Orieux *et al.*, 2000), yet there are studies reporting the opposite as well (Mitchell *et al.*, 1989). *Chapter* 7 describes the first study in humans showing altered gait-related activity in the MLR in PD patients relative to controls. More specifically it shows that cerebral activity is increased in the MLR in PD during motor imagery of gait. Further work is needed to confirm these findings and to gain insight into the relationship between this increased cerebral activity in the MLR and gait performance in PD.

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Nederlandse samenvatting

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Lopen lijkt een simpele beweging. We lopen iedere dag, meestal zonder onze aandacht er bewust bij te houden: lopen in een drukke menigte, rennen om een trein te halen, de trap op lopen, enzovoorts. We kunnen onze loopbewegingen eenvoudig aanpassen aan allerlei nieuwe omstandigheden. Lopen is echter een verrassend complexe beweging, waar veel verschillende systemen bij betrokken zijn. Voorbeelden zijn het visuele systeem, het evenwichtsorgaan, hart & bloedvaten, spieren, gewrichten en het zenuwstelsel. Wanneer één of meerdere van deze systemen niet goed functioneren kunnen loopproblemen ontstaan. Dit is de reden waarom zo veel verschillende ziekten loopproblemen kunnen veroorzaken. Een belangrijk voorbeeld is de ziekte van Parkinson (Box 8.1). Op deze aandoening wordt in dit proefschrift verder ingegaan.

Box 8.1 Loopproblemen bij de ziekte van Parkinson

Loopproblemen zijn een van de belangrijkste symptomen van de ziekte van Parkinson. In de vroege stadia van de ziekte kunnen milde loop- en balansproblemen aanwezig zijn, waaronder een verminderde of afwezige armzwaai, een licht voorovergebogen houding en moeilijkheden met draaien. In de loop van de ziekte wordt het lopen langzamer en komt het karakteristieke looppatroon van Parkinson patiënten naar voren: schuifelende en korte stappen, een verminderde armzwaai en moeite met draaien, waarbij de draaien "en bloc" worden uitgevoerd. Naast deze "continue" loopproblemen, ervaren sommige patiënten korte en plotselinge momenten waarop de voeten als het ware aan de grond blijven plakken ("bevriezen van lopen"). Deze "episodische" loopproblemen komen meer voor naarmate patiënten langer en ernstiger zijn aangedaan. Ze komen ook meer voor na een langdurige behandeling met dopaminerge medicijnen, hoewel ze soms ook voorkomen bij patiënten die nog geen medicatie gebruiken. Bevries episodes duren meestal kort: enkele seconden, maar kunnen soms tot enkele minuten duren, vooral in gevorderde stadia van de ziekte. Ze komen het meest frequent voor wanneer patiënten draaien maken, bij het lopen door een nauwe doorgang, tijdens het starten met lopen, maar soms ook spontaan tijdens gewoon rechtdoor lopen.

Figure 8.1 *Een patiënt met de ziekte van Parkinson door Sir William Richard Gowers uit "A Manual of Diseases of the Nervous System" uit 1886.*

Interessant is dat omgevingsfactoren van invloed zijn op de loopproblemen bij Parkinson. Zo kunnen patiënten met ernstige loopproblemen opeens snel reageren op gebeurtenissen in de omgeving en dan onverwachts goed bewegen. Dit fenomeen wordt "kinesia paradoxica" genoemd en wordt meestal veroorzaakt door emotionele of bedreigende omstandigheden. Aan de andere kant kan het uitvoeren van een dubbeltaak tijdens het lopen juist een negatief effect hebben op de loopproblemen. Zo wordt het lopen moeilijker en slechter wanneer tegelijkertijd een dienblad met glazen wordt gedragen of wanneer gevraagd wordt rekensommen te maken tijdens het lopen.

Loopproblemen bij de ziekte van Parkinson kunnen een grote invloed hebben op de kwaliteit van leven. Ze kunnen bijvoorbeeld resulteren in letsel als gevolg van een valincident. Ook kunnen ze leiden tot een verminderde mobiliteit van de patiënt, met verlies van onafhankelijkheid en een verminderde cardiovasculaire conditie als gevolg. Hoewel sommige loopproblemen verbeterd kunnen worden door het geven van antiparkinson medicatie, is behandeling over het algemeen lastig. Sommige fysiotherapeutische interventies zijn ook effectief, zoals 'cueing': het verbeteren van bewegingen door het aanbieden van ritmische externe prikkels. Een voorbeeld zijn ritmische geluidsprikkels, bijvoorbeeld door een metronoom. Echter, zelfs met optimale medische behandeling blijven veel patiënten aanzienlijk gehandicapt vanwege aanhoudende loopproblemen. De ontwikkeling van nieuwe of betere therapieën is lastig door het nog beperkte inzicht in de hersenprocessen die ten grondslag liggen aan de controle van lopen. In dit proefschrift worden de hersenprocessen die betrokken zijn bij lopen verder bestudeerd, zowel bij gezonde mensen als bij patiënten met de ziekte van Parkinson.

Hoofdstuk 2: Recente vooruitgang in de functionele neuroimaging van lopen
Functionele neuroimaging maakt gebruik van geavanceerde technieken die kunnen vaststellen welke hersengebieden actief zijn tijdens de uitvoering van een specifieke opdracht. Een voorbeeld van een neuroimaging techniek is functional magnetic resonance imaging (fMRI; Box 8.2). De ontwikkeling van dergelijke technieken heeft het mogelijk gemaakt om de hersenprocessen die betrokken zijn bij het lopen van mensen te bestuderen op een manier die voorheen onmogelijk was. Hoewel functionele neuroimaging van het lopen theoretisch aantrekkelijk is, is deze methode echter verre van eenvoudig. Voor de meeste neuroimaging technieken is het namelijk noodzakelijk dat de proefpersonen tijdens het meten van hun hersenactiviteit liggen, en daarnaast niet bewegen. Om deze problemen te omzeilen, zijn er diverse strategieën bedacht. *Hoofdstuk 2* bespreekt hoe elk van die strategieën heeft bijgedragen aan een beter begrip van de hersenprocessen die betrokken zijn bij de controle van lopen, zowel bij gezonde mensen als bij patiënten met de ziekte van Parkinson. Daarnaast wordt een kritische discussie gegeven van de voor- en nadelen van elk van die verschillende strategieën.

Een eerste aanpak is het meten van hersenactiviteit tijdens de daadwerkelijke uitvoering van het lopen. Dit is mogelijk met slechts enkele neuroimaging technieken: nucleaire neuroimaging technieken zoals SPECT en infraroodspectroscopie. Een voordeel van het meten van hersenactiviteit tijdens de daadwerkelijke uitvoering van de loopactiviteit is dat het direct inzicht geeft in de hersengebieden die actief zijn tijdens lopen. Er zijn echter ook nadelen. Zo is het bij het bestuderen van de uitvoering van lopen niet mogelijk om te onderscheiden of de waargenomen veranderingen in hersenactiviteit veroorzaakt worden door de motorische output of door het verwerken van sensorische input. Een alternatieve aanpak is het meten van hersenactiviteit tijdens het plannen van lopen voorafgaand aan het daadwerkelijke starten met de loopactiviteit. Dit is mogelijk met behulp van infraroodspectroscopie en elektroencephalografie (EEG). Een voordeel van deze strategie is dat er minimale effecten zijn van sensorische input aangezien de meting plaatsvindt vóór het starten van het feitelijke lopen. Nadelen zijn echter dat met deze technieken niet nauwkeurig is vast te stellen waar de hersenactiviteit zich precies bevindt. Bovendien is het gebruik van EEG lastig vanwege bewegingsartefacten. Een laatste aanpak is het bestuderen van taken die enkele hersenprocessen gemeen hebben met echt lopen, maar zonder dat de proefpersonen daarbij daadwerkelijk hoeven te lopen. Motorische verbeelding is hier een goed voorbeeld van (Box 8.3), maar ook het maken van bijv. herhaalde simpele voetbewegingen hoort hierbij. Motorische verbeelding van lopen heeft praktische voordelen aangezien er geen echte bewegingen bij betrokken zijn en proefpersonen in een liggende positie onderzocht kunnen worden. Het is daarom met deze techniek mogelijk om neuroimaging technieken zoals fMRI en $H_2{}^{15}O$-PET te gebruiken. Dit is belangrijk omdat deze

technieken relatief nauwkeurig kunnen meten waar de hersenactiviteit zich precies bevindt en omdat ze hersenactiviteit kunnen meten in het gehele brein. Een conceptueel voordeel van motorische verbeelding is dat het gebruikt kan worden om de hersenprocessen te bestuderen die betrokken zijn bij het plannen van lopen (Box 8.3). Het maakt de techniek extra nuttig voor onderzoek bij patiënten met loopproblemen ten gevolge van motorische planning, zoals bij de ziekte van Parkinson. In dit proefschrift is daarom motorische verbeelding van lopen gebruikt om de hersenprocessen die betrokken zijn bij de controle van menselijk lopen verder te bestuderen.

Box 8.2 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is een onderzoeksmethode die gebruik maakt van MRI scans (Fig. 8.2) om te onderzoeken welke hersengebieden actief zijn tijdens het uitvoeren van een bepaalde taak. fMRI werd ontwikkeld rond 1990, en is sinds die tijd uitgegroeid tot één van de belangrijkste technieken in de cognitieve neurowetenschappen.

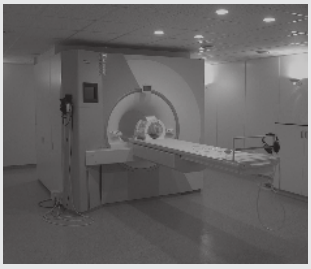

Figure 8.2 *Foto van de MRI scanner die gebruikt is in onze experimenten. Het magnetische veld van deze scanner is 3 Tesla.*

Een voordeel van fMRI is de mogelijkheid om niet-invasief hersensignalen te meten zonder het risico van bijvoorbeeld straling. Daarnaast geeft het de mogelijkheid om relatief nauwkeurig te meten wáár de hersenactiviteit zich precies bevindt. Een nadeel is dat de techniek niet heel nauwkeurig kan bepalen op welk tijdstip de hersenactiviteit plaatsvond. Dit laatste komt omdat fMRI de activiteit van zenuwcellen niet rechtsreeks meet, maar baseert op veranderingen in plaatselijke bloeddoorstroming en zuurstofgebruik in het brein.

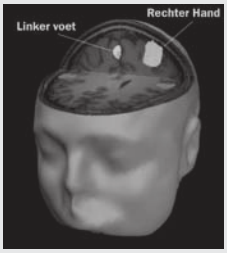

Figure 8.3 *Plaatje van het brein waarin gebieden die statistisch significante activiteit hebben tijdens taak-uitvoering ten opzichte van rust (linker voet bewegingen – rust, of rechter hand bewegingen – rust) zijn aangegeven.*

fMRI kan geen 'absolute' activiteit van hersengebieden meten. Het kan alleen *verschíllen* in hersenactiviteit bepalen tussen meerdere condities (Fig. 8.3). Tijdens het fMRI experiment wordt de proefpersoon daarom gevraagd om afwisselend verschillende taken uit te voeren. Elk van deze taken wordt meerdere keren herhaald en kan worden gescheiden door periodes van rust.

Hoofdstuk 3: Controleren van taakuitvoering bij motorische verbeelding van lopen
Een nadeel van motorische verbeelding van lopen is dat het moeilijk is om de taakuitvoering te controleren. Zo is het is lastig om vast te stellen of proefpersonen in staat zijn zich te verbeelden dat ze lopen en of ze de taak daadwerkelijk uitvoeren. In *Hoofdstuk 3* wordt daarom een nieuw protocol ontwikkeld waarmee het mogelijk is om taakuitvoering te controleren. Hiervoor wordt gebruik gemaakt van zogenaamde 'mentale chronometrie'. Mentale chronometrie omhelst het

Box 8.3 Motorische verbeelding (motor imagery)

Motorische verbeelding is het in gedachten voorstellen van een beweging zonder die beweging ook daadwerkelijk te maken. Er zijn aanwijzingen dat motorische verbeelding gedeeltelijk gebruik maakt van dezelfde hersengebieden die betrokken zijn bij het plannen van echte bewegingen. Deze aanname komt voort uit de bevinding dat er veel overlap is tussen het inbeelden van een beweging, het voorbereiden van een beweging en de feitelijke uitvoering van een beweging. Zo is de tijd die nodig is om een bepaalde bewegingsactie in te beelden sterk gecorreleerd aan de uitvoeringstijd van de echte beweging. Ook hebben fMRI studies laten zien dat gedeeltelijk gebruik wordt gemaakt van vergelijkbare hersengebieden tijdens motorische verbeelding en daadwerkelijke bewegingen. Deze overlap suggereert dat motorische verbeelding, motorische planning en motorische uitvoering gebruik maken van gedeeltelijk gemeenschappelijke processen. Motorische verbeelding wordt daarom gebruikt om de hersenprocessen die betrokken zijn bij het plannen van bewegingen te bestuderen.

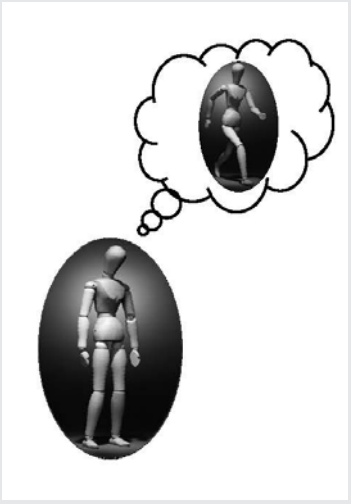

Figure 8.4 *Motorische verbeelding van lopen*

afleiden van de snelheid van informatie verwerking in het zenuwstelsel. Een nauwe overeenkomst tussen de benodigde tijd voor de motorische verbeelding van een beweging en voor de echte uitvoering van diezelfde beweging, suggereert dat proefpersonen in staat zijn om motorische verbeelding uit te voeren. Er zijn verschillende studies die een dergelijke overeenkomst hebben laten zien tussen echte en ingebeelde loopbewegingen. Zo is aangetoond dat, zowel tijdens echt lopen als tijdens ingebeeld lopen, bewegingstijden toenemen met toenemende bewegingsafstand en bewegingsmoeilijkheid (bijvoorbeeld een smallere padbreedte). Het in *Hoofdstuk 3* beschreven protocol maakt gebruik van manipulaties in padbreedte en loopafstand (padlengte) om te controleren of proefpersonen daadwerkelijk de gegeven opdracht uitvoeren. Veertien proefpersonen kregen foto's te zien van een gang met daarin een pad van verschillende lengtes en breedtes. Ze werden gevraagd zich in gedachten voor te stellen om over deze paden heen te lopen. Belangrijk hierbij was dat proefpersonen zich zo levendig mogelijk voor moesten stellen dat ze zelf over de paden liepen, in een eerste-persoons perspectief, alsof hun eigen benen bewogen, maar zonder daarbij echte beenbewegingen te maken. Ingebeelde looptijden werden gemeten door proefpersonen op een knop te laten drukken op het moment dat ze begonnen met het ingebeeld lopen, en men opnieuw de knop in te laten drukken wanneer ze in gedachten het einde van het pad bereikt hadden. De ingebeelde looptijden werden vervolgens vergeleken met de echte looptijden. Het effect van padbreedte en pa-

dlengte op de looptijden was vergelijkbaar voor ingebeeld lopen en echt lopen. Om te onderzoeken of de effecten van padbreedte en padlengte specifiek waren voor motorische verbeelding moesten proefpersonen ook een visuele controletaak uitvoeren. Tijdens deze controletaak stelden ze zich voor dat ze een zwarte schijf over het pad zagen bewegen. Voor deze controletaak werd wel een effect van padlengte, maar geen effect van padbreedte op ingebeelde tijden gevonden. Dit was ook voorspeld, want een passief schuivend object zou immers geen last moeten hebben van variaties in padbreedte, in tegenstelling tot mensen die meer moeite hebben met koorddansen dan gewoon lopen. Het is dus mogelijk om, onder omstandigheden die geschikt zijn voor een neuroimaging omgeving, gedragsmaten te krijgen die een nauwe overeenkomst laten zien tussen ingebeelde en echte looptijden, en die een onderscheid maken tussen motorische en visuele verbeelding. Hierdoor is het mogelijk dit protocol te gebruiken om de hersenprocessen die bij lopen betrokken zijn verder te bestuderen, en dat is wat er in de volgende hoofdstukken is gedaan.

Hoofdstuk 4: Hersengebieden betrokken bij motorische verbeelding van lopen
In *Hoofdstuk 4* wordt bestudeerd welke hersengebieden betrokken zijn bij motorische verbeelding van zowel normaal lopen als het lopen over een heel nauw pad (het zogenaamde "precisielopen", hetgeen een heel nauwkeurige plaatsing van de voeten en een verhoogde controle van de balans vereist). Hierbij is gebruik gemaakt van fMRI (Box 8.2). De hersenactiviteit werd gemeten bij 16 gezonde proefpersonen terwijl ze zich voorstelden dat ze over paden liepen van twee verschillende breedtes (een breed pad van 27 cm, of een smal pad van 9 cm breed). De hersenactiviteit tijdens de motorische verbeelding van het lopen werd vergeleken met de activiteit tijdens een visuele controletaak. De taakuitvoering tijdens motorische verbeelding van lopen werd gecontroleerd door het meten van ingebeelde looptijden. Daarnaast werd de specificiteit van de hersenactiviteit tijdens motorische verbeelding van lopen getest door het te vergelijken met de hersenactiviteit tijdens motorische verbeelding van handbewegingen. Motorische verbeelding van lopen resulteerde in verhoogde hersenactiviteit onder andere links en rechts bovenin de premotore schors, in de bovenste pariëtale kwab en in het linker putamen. De verhoogde hersenactiviteit lag vlak bij gebieden die betrokken zijn bij motorische verbeelding van handbewegingen, maar kon daar wel duidelijk van onderscheiden worden. Deze bevindingen suggereren dat motorische verbeelding van lopen specifieke reacties in het motorische systeem opwekt. Een andere belangrijke bevinding was dat de verhoogde nauwkeurigheid die nodig is voor het verbeelden van lopen over een smal pad resulteerde in een verhoogde hersenactiviteit links en rechts in de bovenste pariëtale kwab en in de rechter middelste verhoging van de occipitale schors. Dit laat zien dat bij precies lopen hersengebieden betrokken zijn die liggen buiten de primaire motore gebieden.

Hoofdstuk 5: Motorische verbeelding van voetbewegingen en lopen: effecten op de prikkelbaarheid van de hersenschors
Hoofdstuk 4 toonde aldus aan dat de premotore hersenschors actief is tijdens motorische verbeelding van lopen. In *Hoofdstuk 5* wordt onderzocht of motorische verbeelding ook leidt tot een verhoging van de prikkelbaarheid van de baan die loopt van de motorische hersenschors naar het ruggenmerg (corticospinale baan). Dit is mogelijk met behulp van de techniek transcraniële magnetische stimulatie (TMS; Box 8.3). Aangezien het bewijs voor een verhoging van corticospinale prikkelbaarheid tijdens motorische verbeelding van beenbewegingen nog erg beperkt is, is naast motorische verbeelding van lopen ook de motorische verbeelding van een simpele voetbeweging bestudeerd. TMS werd toegepast op de primaire motorische schors van 16 gezonde proefpersonen terwijl ze zich voorstelden dat ze hun voet naar hun knie optrokken (Experiment I) en dat ze liepen (Experiment II). De mate van corticospinale prikkelbaarheid werd bepaald door de spierreactie van een beenspier en een handspier als gevolg van de TMS puls te meten. De spierreacties tijdens motorische verbeelding werden vergeleken met die tijdens een visuele controletaak. Ingebeelde vo-

etbewegingen verhoogden de spierreacties in zowel de beenspier als de handspier ten opzichte van de visuele controletaak. Het effect was groter in de beenspier dan in de handspier. Deze bevindingen suggereren dat ingebeelde voetbewegingen resulteren in een verhoging van de prikkelbaarheid van de corticospinale baan. Motorische verbeelding van *lopen* had geen effect op de prikkelbaarheid van de corticospinale baan. Dit laatste komt mogelijk door de timing van de TMS pulsen. Het was namelijk met het gebruikte protocol niet mogelijk om de TMS pulsen tijdens een specifieke fase van de loopcyclus te geven. Verder onderzoek moet daarom uitwijzen of de prikkelbaarheid van de corticospinale baan alleen verhoogd is tijdens bepaalde fases van de loopcyclus.

Box 8.4 Transcraniële magnetische stimulatie

Transcraniële magnetische stimulatie (TMS) werd in 1985 geïntroduceerd door de onderzoeksgroep van Prof. Barker (Fig. 8.5). Het is een niet-invasieve onderzoeksmethode om hersencellen te activeren. TMS maakt gebruik van een elektromagnetische spoel die boven het hoofd van de proefpersoon wordt gehouden. Wanneer er stroom door de spoel loopt, wekt dit een magnetisch veld op, dat de hoofdhuid en schedel heel gemakkelijk passeert. Door het magnetische veld snel te veranderen kunnen zwakke elektrische stromen opgewekt worden in het naburige hersenweefsel (elektromagnetische inductie). Dit maakt het mogelijk om met minimaal ongemak hersenactiviteit op te wekken.

Wanneer TMS wordt toegepast over de motorische hersenschors, dan veroorzaakt dit een reactie die direct gezien kan worden: een korte spier aanspanning (Fig. 8.6). Wanneer de spierrespons die opgewekt kan worden met TMS elektrisch wordt gemeten, spreekt men van een motor-evoked potential (MEP). De amplitude van de MEP geeft informatie over de prikkelbaarheid van het corticospinale systeem. TMS-onderzoek levert wezenlijk andere informatie dan bijvoorbeeld fMRI, en heeft daarmee in belangrijke mate bijgedragen aan ons begrip van de sturing van lichaamsbewegingen.

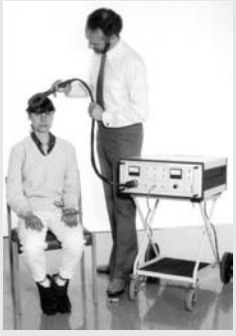

Figure 8.5 *Anthony T. Barker met de stimulator die gebruikt werd om TMS voor de eerste keer toe te passen.*

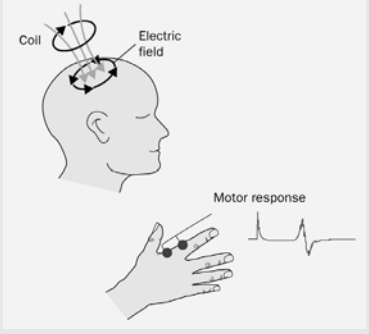

Figure 8.6 *Het basale principe van TMS. De figuur is aangepast van (Kobayashi and Pascual-Leone, 2003).*

Hoofdstuk 6: Hersengebieden betrokken bij motorische verbeelding van lopen bij de ziekte van Parkinson

In *Hoofdstuk 6* wordt met behulp van motorische verbeelding van lopen onderzocht welke hersengebieden betrokken zijn bij het plannen van lopen bij de ziekte van Parkinson. Hersenactiviteit werd gemeten met behulp van fMRI bij 19 Parkinson patiënten en 21 gezonde controlepersonen. De proefpersonen werd gevraagd om het in Hoofdstuk 3 ontwikkelde protocol uit te voeren. Dit protocol bestond uit motorische verbeelding van lopen en een visuele controletaak. Daarnaast werd de daadwerkelijke uitvoering van lopen bestudeerd met behulp van een drukgevoelige loopmat. Zoals verwacht hadden Parkinson patiënten tijdens de daadwerkelijke uitvoering van lopen een kleinere stap lengte dan controles. Tijdens motorische verbeelding van lopen waren de effecten van padbreedte en padlengte op ingebeelde looptijden vergelijkbaar voor patiënten en controles. Ook waren er geen verschillen in ingebeelde looptijden tussen beide groepen. Deze bevindingen suggereren dat Parkinson patiënten en controles even goed in staat waren om motorische verbeelding van lopen uit te voeren. Om dit voor elkaar te krijgen, werden bij Parkinson patiënten echter wel andere hersengebieden ingeschakeld. Zo was er bij Parkinson patiënten een relatieve afname van hersenactiviteit zowel links als rechts in de supplementaire motorische schors, in de bovenste pariëtale kwab en in het cerebellum. Daarnaast was er een relatieve toename van hersenactiviteit in de hersenstam. Deze bevindingen suggereren dat deze hersengebieden betrokken zijn bij de problemen met het plannen van lopen bij patiënten met de ziekte van Parkinson.

Conclusies

Motorische verbeelding is een waardevolle aanpak om meer inzicht te krijgen in de hersenstructuren die betrokken zijn bij lopen, maar het is wel belangrijk om daarbij de taakuitvoering tijdens het experiment te controleren. Ons nieuw ontwikkelde protocol maakt het mogelijk om de uitvoering van motorische verbeelding van lopen te kwantificeren tijdens een neuroimaging experiment. Met behulp van dit protocol werd gevonden dat corticale structuren buiten de primaire motorische gebieden betrokken zijn bij het voorstellen van loopbewegingen wanneer een precieze plaatsing van de voet noodzakelijk is. Verder werd gevonden dat - hoewel de uitvoering vergelijkbaar is - motorische verbeelding van lopen ondersteund wordt door verschillende netwerken in de hersenen van Parkinson patiënten en gezonde personen.

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Curriculum Vitae

Maaike Bakker was born on the 20th of October 1979 in Laren, the Netherlands. She finished secondary education at the Erfgooiers College in Huizen in 1997. That same year she started studying Medical Biology at the Vrije Universiteit in Amsterdam. As part of her Medical Biology study, she performed two research traineeships at the Vrije Universiteit in Amsterdam: one at the Department of Neuro-Anatomy and the other at the Department of Movement Sciences. Her third research traineeship was at the Department of Neurology at the Radboud University Medical Centre Nijmegen. After graduation in 2002, she was employed as a research assistant at the Department of Audiology and Neurootology at the University of Basel (Switzerland). In 2003, she was given the opportunity to go back to the Department of Neurology in Nijmegen, to start working as a junior investigator. In 2004, she started working on the projects of this thesis at the Donders Institute - Centre for Cognitive Neuroimaging in Nijmegen.

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