

**Cognitive control of gait and balance
in patients with chronic stroke and
Parkinson's disease**

Katrijn Smulders

The research presented in this thesis was carried out at the departments of Neurology and Rehabilitation at the Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center in Nijmegen, the Netherlands. The research was supported by grants of the HAN University of Applied Sciences, Michael J. Fox Foundation, ZonMw and the Stichting Internationaal ParkinsonFonds.

Financial support for publication of this thesis was kindly provided by the Stichting Internationaal ParkinsonFonds, Stichting Alkemade-Keuls Fonds, UCB Pharma B.V., Ipsen farmaceutica B.V., AbbVie B.V., HAN Sport en Bewegen and Parkinson vereniging

Lay-out: Mark de Niet, ScienceSupport
Cover design: Marijke Steinmann
Printed by Ipskamp Drukkers B.V.

ISBN 978-94-91027-92-5

© Katrijn Smulders 2014

Except chapters 2, 5, 7 (Elsevier). All rights reserved. No parts of this thesis may be reproduced or trans-mitted in any form or by any means, electronic or mechanical, including photocopy, recording or otherwise without permission of copyright owners or the author.

Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus
prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen
op woensdag 21 mei 2014
om 14.30 uur precies

door

Katrijn Smulders
geboren op 28 december 1978
te Eindhoven

Promotoren:

Prof. dr. B.R. Bloem

Prof. dr. A.C.H. Geurts

Copromotoren:

Dr. R.A.J. Esselink

Dr. B.J.M. de Swart

Manuscriptcommissie:

Prof. dr. M.G.M. Olde Rikkert

Prof. dr. J. Duysens

Prof. dr. G. Kwakkel (Vrije Universiteit, Amsterdam)

Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease

Doctoral Thesis

To obtain the degree of doctor
from Radboud University Nijmegen
on the authority of
Rector Magnificus prof. dr. S.C.J.J. Kortmann,
according to the decision of the Council of Deans
to be defended in public on
Wednesday, May 21, 2014
at 14.30 hours

by

Katrijn Smulders

Born on December 28, 1978
in Eindhoven

Supervisors:

Prof. dr. B.R. Bloem

Prof. dr. A.C.H. Geurts

Co-supervisors:

Dr. R.A.J. Esselink

Dr. B.J.M. de Swart

Doctoral Thesis Committee:

Prof. dr. M.G.M. Olde Rikkert

Prof. dr. J. Duysens

Prof. dr. G. Kwakkel (VU University, Amsterdam)

Contents

Chapter 1.	General introduction	9
Part I	Patients with chronic stroke	
Chapter 2	Community-dwelling people with chronic stroke need disproportionate attention while walking and negotiating obstacles	27
Chapter 3	Evaluating the concept of gait adaptability training for improving gait adjustments and associated attentional demands after stroke	43
Part II	Patients with Parkinson's disease	
Chapter 4	Assessment of dual tasking has no clinical value for fall prediction in Parkinson's disease	65
Chapter 5	Involvement of specific executive functions in mobility in Parkinson's disease	83
Chapter 6	Trait impulsivity is associated with the risk of falls in Parkinson's disease	93
Chapter 7	Freezing of gait in Parkinson's disease is related to impaired motor switching during stepping	111
Chapter 8	Postural inflexibility in PD: Does it affect compensatory stepping?	123
Chapter 9	Summary	145
Chapter 10	General discussion	153
	Nederlandse samenvatting	169
	Dankwoord	175
	Curriculum Vitae	181
	List of publications	183
	Donders Graduate School for Cognitive Neuroscience Series	184
	Dissertations of the Parkinson Centre Nijmegen	193

Chapter 1

General introduction



Introduction

Gait and postural stability

Every day we take between 6,000 and 13,000 steps while walking in and around our house, at work, or while performing household and leisure-time activities.¹ Although walking can be accomplished by vertebrates without a head but with a brainstem,² this literally and figuratively results in “running around like a chicken with its head cut off”. Cortical and subcortical brain structures enable us to use sensory and cognitive information to guide our movements. Thus, although we only need our spinal cord to generate a locomotion pattern, the higher brain regions allow for walking that is goal-directed and adjusted to environmental demands.⁴

One of the challenges of walking is to keep the body in a stable position. At least part of the time, the total weight of the body needs to be balanced on an area as small as one foot. To stay upright and maintain a stable walking pattern, balance control mechanisms are needed. This is already true for walking in predictable environments such as the examination room of the doctor. However, when walking outside, one also needs to pay attention to traffic, to irregularities on the ground, or to the conversation with a friend. Although we may not be aware of it, all these disturbances call for cognitive control. Dealing with these daily life challenges of walking inadequately can result in stumbling, tripping, or even a fall.

Nonetheless, we generally do not experience walking to be difficult. Our brain is well adapted to the requirements of everyday walking, and falls seldom occur in healthy young adults. This is, however, different for patients with neurological disorders that impair gait and balance. For example, over a period of six months, 73% of the patients after a stroke and 50% of the patients with Parkinson's disease (PD) experience one or multiple falls.^{5,6}

In this thesis, the role of cognitive control in gait and balance is studied in both stroke and PD patients. First, I will introduce the topic of cognitive control of gait in stroke patients, followed by a section on the interaction between cognitive and motor deficits in PD.

Gait difficulty and postural instability in stroke

A stroke is caused by ischemia (lack of blood flow) in the brain or by intracranial hemorrhage (bleeding). Depending on the site of the brain damage, a stroke results in sensory, motor, and/or cognitive impairments affecting daily life activities, even in the chronic phase (> 6 months post stroke).

Damage to brain areas that are directly involved in, or that are part of

networks of movement control lead to muscle weakness, spasticity and abnormal (synergistic) movement patterns.⁷ As for gait, these motor deficits cause slowing of walking speed and asymmetry between the affected and unaffected leg.⁸ Asymmetry also results in unequal weight bearing and unequal contribution of both legs to balance control during quiet stance. Such postural asymmetry and increased body sway are characteristic of unperturbed stance in stroke patients.^{9,10}

A common aspect of impaired gait in stroke is a 'drop foot'. As a consequence of paresis of the ankle dorsiflexors, patients have problems lifting their foot during gait, which is particularly important during the swing phase of a step. Insufficient clearance of the foot during walking can cause tripping or stumbling. To prevent this, patients adjust their walking pattern, for instance, by reverting to 'circumduction' of the leg.

Besides direct effects of damage to motor areas, deficits in cognitive and sensory functions can severely impair gait and postural stability. Hence, lesions in brain areas involved in cognitive control and sensorimotor integration can further affect mobility in stroke patients. The specific site of the brain lesion might, therefore, be expected to be important for the severity of gait difficulty and postural instability. Unfortunately, studies exploring the association of gait and balance control with lesion site are scarce and inconclusive.¹¹⁻¹⁴ In this thesis, stroke patients are therefore studied based on the severity of their deficits instead of lesion site, with emphasis on the functional consequences of their motor impairments. Moreover, only patients that were able to walk independently were included.

Automaticity of gait and postural stability

Although walking and maintaining postural stability are seemingly automatic, research has shown that even healthy young persons need to cognitively control these tasks.^{15,16} Cognitive control of movement is nicely illustrated by motor learning processes. For instance, when learning to shoot a ball through a hoop, relatively much attention is paid in the first tries to the positioning of the hands, the amount of force to apply to the ball, where to aim, and so on. With practice, the need to pay attention to all these aspects strongly diminishes, leaving room for the attentional capacity to be involved in other cognitive processes, such as tactical decisions in the game.

Classical theories of attention assume that its capacity is limited.¹⁷ When the tasks at hand exceed the available resources, performance of at least one of the tasks decays (see Box 1). If a task does not demand attention (in other words, if a task is fully automatic), addition of a secondary task will not lead to a decline

in performance of either one of the tasks. The amount of attention needed to successfully perform a task can be measured using a dual task paradigm. Participants are instructed to keep up the performance of both tasks. The deterioration in performance of task A while executing a second task B, relative to the performance of task A in isolation, indicates the level of automaticity of task A. One should also assess the change in performance of task B to interpret the level of automaticity of either task. When no change in the performance of task A is observed, but the performance of task B is affected under dual task compared to single task conditions, this also indicates that task A requires at least some attention.

Reduced automaticity, or increased cognitive control, is a common consequence of motor impairments. Following injury, rehabilitation focuses on relearning of motor skills as well as learning new movement strategies to compensate lost functions. For instance, patients with a stroke who have (partly) lost their ambulation capacity will need to learn to walk again given the new, altered state of the brain and the body. Similar to learning a new skill, the first phases of re-learning require the patients to allocate a major part of their attentional resources to control their posture and movements of the limbs.

A considerable number of stroke patients eventually regain the ability to walk.¹⁸ However, the need to pay extra attention to walking is a commonly reported complaint, even in well-recovered patients. Seemingly minor gait impairments may have a significant impact on walking under complex conditions such as those encountered in daily life situations. This includes the ability to walk while talking, and to quickly adjust the walking pattern when sudden obstacles appear or external perturbations occur.

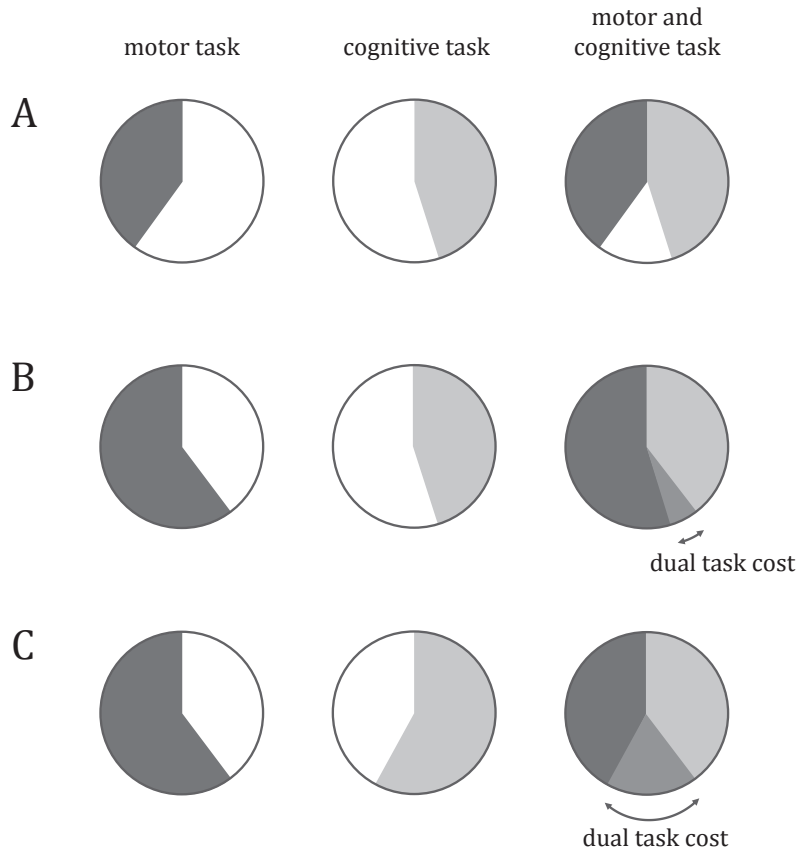
Loss of gait automaticity presumably hampers mobility in all patient groups with motor impairments, increasing the need for cognitive control. In the next section, we will address this issue from the perspective of patients with Parkinson's disease; a neurodegenerative condition well known for its combination of motor and cognitive deficits.

Gait difficulty and postural instability in PD

While a stroke leads to a sudden loss of brain functions, Parkinson's disease (PD) is a slowly progressive condition. Degeneration of dopaminergic cells in the substantia nigra cause dopamine depletion in the (dorsal) striatum (see Box 2). Dopaminergic neurons in the basal ganglia modulate the activity of the thalamus, and loss of dopamine results in exaggerated inhibition of the thalamus, which reduces its input to the cortex. The characteristic slowness of movement in PD (bradykinesia) can, thus, directly be explained by the dopamine depletion in the

neural loops between the basal ganglia and the motor cortex.

Box 1: Attentional demands in three dual task situations.



A. The attentional demands for a relatively easy motor task (e.g. walking) together with an easy secondary cognitive task (e.g. counting back from 100 in steps of three) results in a situation in which both tasks together do not exceed the available attentional capacity. In this situation, there are no dual task costs.

B. If the motor task is complex, for instance when walking over uneven terrain, attentional demands increase. Also in patients with motor deficits, an easy motor task is more attention-demanding because of reduced automaticity. In this situation, the addition of the easy cognitive task results in dual task costs. Either the motor or the cognitive task performance is affected, or both.

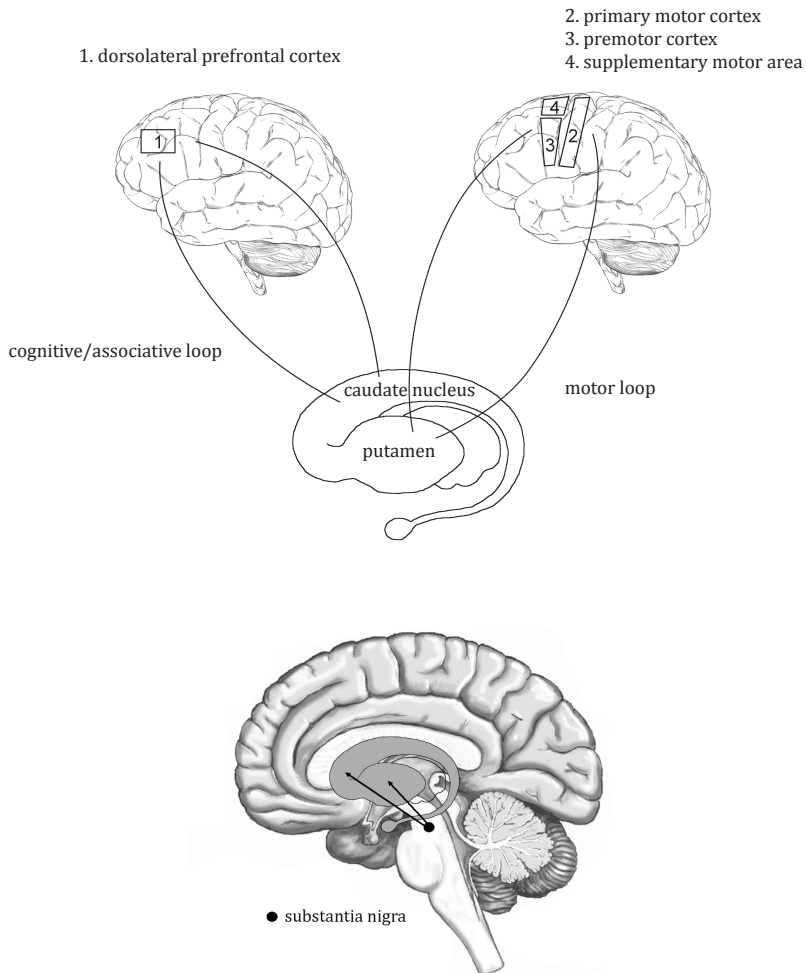
C. When the attentional demands of the cognitive task are increased as well, the dual task costs increase further. This happens when the cognitive task is more complex (e.g. counting back by 7's), or when the subject has cognitive impairments. Which task becomes most affected depends on the priority setting. Alternatively, performance during dual tasking is dependent on the ability to switch between both tasks.

In parkinsonian gait, bradykinesia is reflected by a shortened step length and a reduced gait speed.¹⁹ Because bradykinesia is associated with dopamine loss, restoration of dopamine levels by medication is beneficial to these gait parameters. Another common aspect of parkinsonian gait is increased left-right asymmetry and stride-to-stride variability.²⁰ However, gait asymmetry and variability do not respond well to dopaminergic medication. This has led to the suggestion that these gait parameters originate from non-dopaminergic pathways.²¹

While slowness and variability of walking are continuously present in patients with PD, episodic gait disturbances are also observed. Patients may have difficulty with the initiation or continuation of movement and experience episodes of 'freezing' of gait. During such freezing episodes, the patient feels that his feet are 'glued' to the ground. Freezing of gait episodes particularly occur during initiation of walking and turning.²² Such motor blocks are seriously incapacitating and often lead to falls.^{23,24} Freezing of gait most commonly occurs when patients are in an "off" period (without dopaminergic medication). This type of freezing of gait is consequently relieved by taking dopaminergic medication. However, in some patients freezing of gait episodes are unresponsive to dopamine, or can even be triggered by dopaminergic medication.²⁵

Besides gait impairments, postural instability is a hallmark of PD, inducing imbalance and falls. Balance recovering responses are hypometric in PD^{26,27} and when a step is needed, extra preparatory processes to ensure postural stability are required.²⁸ Moreover, PD patients lack the ability to flexibly modify their motor responses to the context of the task.²⁹⁻³³ Similar to gait variability, postural instability is not responsive to treatment with dopaminergic drugs.

As described in the previous paragraph, gait and balance deficits increase the demand on cognitive control processes. But what if cognitive functions are also impaired? Although classified as a predominant movement disorder, cognitive impairments exist even in the earliest stages of PD.^{34,35} Specifically, PD patients experience problems with tasks that demand set switching³⁶⁻³⁸ and/or inhibition.^{39,40} Hence, besides motor symptoms, cognitive impairments can hamper gait and postural stability. Unfortunately, most studies that focused on this interaction were correlational in nature. Whether and how cognitive impairments may cause problems with gait and postural stability remains to be elucidated.

Box 2: Connections of the basal ganglia.

The basal ganglia project to and receive input from different parts of the cortex. In the upper part of this figure a schematic representation of the motor and cognitive loops are shown. According to Alexander et al.,³ the motor loop consists of connections between the putamen and the (pre)motor areas. The cognitive loop connects the caudate nucleus and the dorsolateral prefrontal cortex. Note that these loops also comprise the globus pallidus and the thalamus, which are not shown in this model.

In the lower part the dopamine pathway from the substantia nigra to the basal ganglia is depicted by the black arrows. Neurons in the substantia nigra (pars compacta) degenerate in Parkinson's disease, causing a lack of dopamine to the basal ganglia. In the early stages of the disease, the dorsal parts of the basal ganglia (i.e. putamen) are deprived of dopamine.

Cognitive processes underlying the control of gait and balance

Although dual task paradigms are useful for the assessment of cognitive load when performing motor tasks, the underlying concept of *attention* remains hard to define. In order to better understand the role of cognition in motor control, studying specific underlying cognitive processes might prove more fruitful.

Cognitive control is closely related to attention, including the ability to focus attention to the task(s) at hand and to disregard irrelevant (distracting) stimuli. Setting a goal, determining the plan to achieve this goal, monitoring whether the movement is executed according to plan, allocating the appropriate amount of attention to the task, and inhibiting irrelevant processes, are all elements of the proper cognitive influence on effective motor control. In the literature, such higher-level control processes are referred to as ‘executive functions’.

Three separate components of cognitive control have been identified: working memory, set switching and inhibition.⁴¹ First, *working memory* reflects the ability to temporarily store and update information.⁴² Ongoing movements require continuous monitoring to adjust the movements to changes in the environment. When involved in multiple tasks at the same time, these tasks will consume the limited cognitive resources of working memory. Second, *set switching* is defined as the ability to flexibly alter one’s behavior when relevant changes occur in the predefined goal or in the environment.^{43,44} Moving around requires switching between different movement sets, for example alternating between walking, turning, standing up and sitting down. In addition, switching between attentional sets is necessary, for example when changing one’s focus from irregularities in the walkway to the direction of walking.

In the remainder of this introduction, set switching and inhibition will be elaborated further, because these cognitive processes will be addressed in this thesis.

Set switching

Set switching performance reflects the ability to flexibly switch between tasks or attentional sets. A set arises when a task is repeated several times, generally resulting in quicker responses or lower error rates.⁴⁴ For instance, consider the following task: the letter-number combination “A5” is presented with the instruction to name the letter that is shown, ignoring the number. With practice, reaction time goes down. One is ‘set’ to letter naming. When the instruction is then changed to naming the number, thereby ignoring the letter, responses will initially be slower. The established letter-naming task set needs to be overruled, requiring extra cognitive processing which (temporarily) slows the responses.

Although set switching is traditionally associated with prefrontal activity,

set switching is impaired in PD due to basal ganglia dysfunction.⁴⁵⁻⁴⁷ The basal ganglia are involved in the selection of the appropriate action and in the inhibition of competing actions.⁴⁸ To this end, the basal ganglia interact with the cortex through parallel circuits subserving motor, cognitive, and emotional functions.³ The different cortical areas provide the basal ganglia with information on internal goals and external circumstances, thereby enabling the selection of the appropriate action. Thus, switching between actions requires intact functioning of the basal ganglia.⁴⁶

In PD, dopamine loss in the basal ganglia hampers this flexibility.⁴⁹ Set switching performance has been studied for switching between finger movement sequences as well as for switching between abstract rules.⁵⁰⁻⁵³ However, it is questionable how well these studies translate to the role of set switching in locomotor behavior. Theoretically, gait initiation can be viewed as a change from quiet standing to walking, which is a change in motor set. The role of set switching in gait difficulty and postural instability in PD has received only minor attention. A few studies in the 90's aimed to investigate this subject. For example, in one study subjects underwent a series of repeated postural perturbations in the forward-backward direction, suddenly followed by a rotational perturbation demanding a different muscle activation pattern.²⁹ PD patients adapted less quickly to the new situation compared with their healthy controls, which was interpreted as postural inflexibility.

Another, more recent, line of research focused on the neuropsychological profiles of patient groups with gait difficulty and postural instability. Specifically, research on patients with freezing of gait has raised interesting findings, revealing attentional set switching deficits in this specific subgroup of PD patients.⁵⁴

Inhibition

A second key aspect of cognitive impairment in PD is inhibitory control. When inhibitory processes fail, behavior becomes impulsive. Impulsive behavior is manifested by premature responses, impaired ability to stop actions, or making rapid decisions or impulsive choices.^{55,56}

In PD, impulsive behavior is more common when compared to healthy peers. Impulsive-compulsive disorders (ICD) are present in 13.6% of PD patients,⁵⁷ and these are often caused by use of dopaminergic medication.⁵⁸ Although dopamine treatment improves main motor symptoms of the disease by restoring the dopamine depletion in the dorsal striatum, the additional dopamine can overdose the ventral striatum, where dopamine levels are relatively intact. Since the ventral striatum plays a role in the reward system, the extra dopamine results in behavior that is more sensitive to rewards, possibly inducing impulsive

choice.^{58,59}

Impulsive behavior in combination with gait and balance impairments intuitively has deleterious consequences. Ahlskog⁶⁰ (p. 1227) worded this as follows: “[...] experience in the clinic reveals that some of the worst fallers are those who impulsively jump from their chair or turn without thinking.”

Outline of this thesis

The general aim of this thesis is to further increase our understanding of the cognitive control of gait and balance in patients with chronic stroke as well as in patients with PD. My thesis is divided into two parts. The first part consists of chapters 2 and 3. In these chapters, two studies are presented concerning dual task effects in well-recovered, patients with stroke. In **chapter 2**, I aimed to measure the attentional demands of walking in daily life by using a task requiring to step over a suddenly appearing obstacle. The addition of a second, cognitive task enabled us to quantify the amount of attention needed for this challenging gait task. In **chapter 3**, the same dual task was used to assess the effect of a novel training method for stroke patients using an instrumented treadmill with augmented feedback in the form of visual targets and obstacles (C-Mill) in an attempt to improve the adaptability of gait. In this study, we could assess whether a potential training benefit on the obstacle avoidance task was (partly) due to a decrease in attentional demands.

The second part of this thesis focuses on patients with PD. In **chapter 4**, I again used the dual task paradigm applied in the first part to find out whether dual task performance can be used to predict fall risk in PD patients. In the next chapters I zoom in on the cognitive processes underlying attention control during movement. In **chapter 5**, I aimed to disentangle which of the three executive cognitive functions (i.e. working memory, set switching, inhibition) is associated with functional mobility in PD. In **chapter 6** the focus is on the relationship between inhibitory control and fall risk in patients with PD. In this chapter, the impact of impulsive personality traits on fall risk is investigated.

In chapters 7 and 8, I specifically investigated the role of set switching in gait and balance problems in PD. First, I investigated whether a set switching deficit is apparent in voluntary stepping responses (**chapter 7**). For this purpose, I used a cognitive set switching paradigm and had patients make a step instead of using verbal responses or key presses commonly used in studies focusing at cognitive deficits. Because for balance control, stepping responses are reactive rather than voluntary, I also designed a series of postural perturbations to assess set-switching ability. In **chapter 8**, I describe an experiment in which postural flexibility was assessed in PD patients using the Radboud Falls simulator. The

Radboud Falls simulator is a movable platform that can translate at different accelerations, imposing either large postural perturbations (invoking stepping responses) or small perturbations (allowing feet-in-place responses). I compared stepping responses preceded by a series of feet-in-place perturbations (inducing a switch in postural set), with stepping responses that were part of a series of other stepping responses (continuing the same postural set). This procedure allowed me to assess whether PD patients are able to flexibly switch and adjust their motor responses to the imposed perturbations.

This thesis ends with a summary (**chapter 9**) and general discussion in **chapter 10**, where I will critically reflect and integrate the findings of the previous chapters and provide new perspectives for research and treatment.

References

1. Tudor-Locke CE, Myers AM. Methodological considerations for researchers and practitioners using pedometers to measure physical (ambulatory) activity. *Res Q Exerc Sport*. Mar 2001;72(1):1-12.
2. Whelan PJ. Control of locomotion in the decerebrate cat. *Prog Neurobiol*. Aug 1996;49(5):481-515.
3. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 1986;9:357-81.
4. Jacobs JV, Horak FB. Cortical control of postural responses. *J Neural Transm*. 2007;114(10):1339-48.
5. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. *BMJ*. Jul 8 1995;311(6997):83-6.
6. Pickering RM, Grimbergen YA, Rigney U, et al. A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov Disord*. Oct 15 2007;22(13):1892-900.
7. Knutsson E, Richards C. Different types of disturbed motor control in gait of hemiparetic patients. *Brain*. Jun 1979;102(2):405-30.
8. Patterson KK, Parafianowicz I, Danells CJ, et al. Gait asymmetry in community-ambulating stroke survivors. *Arch Phys Med Rehabil*. Feb 2008;89(2):304-10.
9. Geurts AC, de HM, van NI, Duysens J. A review of standing balance recovery from stroke. *GaitPosture*. 2005;22(3):267-81.
10. Van Asseldonk EH, Buurke JH, Bloem BR, et al. Disentangling the contribution of the paretic and non-paretic ankle to balance control in stroke patients. *Exp Neurol*. Oct 2006;201(2):441-51.
11. Alexander LD, Black SE, Patterson KK, Gao F, Danells CJ, McIlroy WE. Association between gait asymmetry and brain lesion location in stroke patients. *Stroke*. Feb 2009;40(2):537-44.
12. Dromerick AW, Reding MJ. Functional outcome for patients with hemiparesis, hemihypesthesia, and hemianopsia. Does lesion location matter? *Stroke*. Nov 1995;26(11):2023-6.
13. Miyai I, Suzuki T, Kang J, Kubota K, Volpe BT. Middle cerebral artery stroke that includes the premotor cortex reduces mobility outcome. *Stroke*. Jul 1999;30(7):1380-3.
14. De Laat KF, van den Berg HA, van Norden AG, Gons RA, Olde Rikkert MG, de Leeuw FE. Microbleeds are independently related to gait disturbances in elderly individuals with cerebral small vessel disease. *Stroke*. Feb 2011;42(2):494-7.
15. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture*. 2002;16(1):1-14.
16. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329-42.
17. Kahneman D. Attention and task interference. In: Kahneman D, ed. *Attention and Effort*. Englewood-Cliffs, New Jersey: Prentice-Hall; 1973:178-201.
18. Preston E, Ada L, Dean CM, Stanton R, Waddington G. What is the probability of patients who are nonambulatory after stroke regaining independent walking? A systematic review. *Int J Stroke*. Dec 2011;6(6):531-40.

19. Morris ME, Iansek R, Matyas TA, Summers JJ. The pathogenesis of gait hypokinesia in Parkinson's disease. *Brain*. Oct 1994;117 (Pt 5):1169-81.
20. Hausdorff JM. Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos*. Jun 2009;19(2):026113.
21. Lord S, Baker K, Nieuwboer A, Burn D, Rochester L. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? *J Neurol*. Apr 2011;258(4):566-72.
22. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur J Neurol*. Jul 2003;10(4):391-8.
23. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA. Predictors of future falls in Parkinson disease. *Neurology*. Jul 13 2010;75(2):116-24.
24. Moore O, Peretz C, Giladi N. Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. *Mov Disord*. Nov 15 2007;22(15):2192-5.
25. Espay AJ, Fasano A, van Nuenen BF, Payne MM, Snijders AH, Bloem BR. "On" state freezing of gait in Parkinson disease: a paradoxical levodopa-induced complication. *Neurology*. Feb 14 2012;78(7):454-7.
26. Jacobs JV, Horak FB. Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease. *Neuroscience*. Aug 25 2006;141(2):999-1009.
27. King LA, Horak FB. Lateral stepping for postural correction in Parkinson's disease. *Arch Phys Med Rehabil*. Mar 2008;89(3):492-9.
28. King LA, St George RJ, Carlson-Kuhta P, Nutt JG, Horak FB. Preparation for compensatory forward stepping in Parkinson's disease. *Arch Phys Med Rehabil*. Sep 2010;91(9):1332-8.
29. Chong RK, Horak FB, Woollacott MH. Parkinson's disease impairs the ability to change set quickly. *J Neurol Sci*. 2000;175(1):57-70.
30. Dimitrova D, Horak FB, Nutt JG. Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *J Neurophysiol*. Jan 2004;91(1):489-501.
31. Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. *J Neurol Sci*. 1992;111(1):46-58.
32. Schieppati M, Nardone A. Free and supported stance in Parkinson's disease. The effect of posture and 'postural set' on leg muscle responses to perturbation, and its relation to the severity of the disease. *Brain*. Jun 1991;114 (Pt 3):1227-44.
33. Smith BA, Jacobs JV, Horak FB. Effects of magnitude and magnitude predictability of postural perturbations on preparatory cortical activity in older adults with and without Parkinson's disease. *Exp Brain Res*. Oct 2012;222(4):455-70.
34. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*. 2005;65(8):1239-45.
35. Kudlicka A, Clare L, Hindle JV. Executive functions in Parkinson's disease: systematic review and meta-analysis. *Mov Disord*. Nov 2011;26(13):2305-15.

36. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*. Dec 2001;124(Pt 12):2503-12.
37. Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia*. 1989;27(11-12):1329-43.
38. Owen AM, James M, Leigh PN, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain*. 1992;115 (Pt 6):1727-51.
39. Wylie SA, Ridderinkhof KR, Bashore TR, van den Wildenberg WP. The effect of Parkinson's disease on the dynamics of on-line and proactive cognitive control during action selection. *J Cogn Neurosci*. Sep 2010;22(9):2058-73.
40. Wylie SA, van den Wildenberg W, Ridderinkhof KR, Claassen DO, Wooten GF, Manning CA. Differential susceptibility to motor impulsivity among functional subtypes of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Aug 23 2012.
41. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol*. 2000;41(1):49-100.
42. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4th. New York: Oxford University Press; 2004.
43. Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci*. May 29 2007;362(1481):917-32.
44. Monsell S. Task switching. *Trends in cognitive sciences*. Mar 2003;7(3):134-40.
45. Cools R, Clark L, Robbins TW. Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. *J Neurosci*. Feb 4 2004;24(5):1129-35.
46. Cools R, Ivry RB, D'Esposito M. The human striatum is necessary for responding to changes in stimulus relevance. *J Cogn Neurosci*. Dec 2006;18(12):1973-83.
47. Dang LC, Donde A, Madison C, O'Neil JP, Jagust WJ. Striatal dopamine influences the default mode network to affect shifting between object features. *J Cogn Neurosci*. 2012;24(9):1960-70.
48. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol*. Nov 1996;50(4):381-425.
49. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*. 2003;41(11):1431-41.
50. Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. *Brain*. Apr 1987;110 (Pt 2):361-79.
51. Cools AR, van den Bercken JH, Horstink MW, van Spaendonck KP, Berger HJ. Cognitive and motor shifting aptitude disorder in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. May 1984;47(5):443-53.
52. Hayes AE, Davidson MC, Keele SW, Rafal RD. Toward a functional analysis of the basal ganglia. *J Cogn Neurosci*. 1998;10(2):178-98.
53. Robertson C, Flowers KA. Motor set in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Jul 1990;53(7):583-92.

54. Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. *Mov Disord*. Jun 15 2010;25(8):1000-4.
55. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron*. Feb 24 2011;69(4):680-94.
56. Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends in cognitive sciences*. Jan 2012;16(1):81-91.
57. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. May 2010;67(5):589-95.
58. Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. *Brain*. May 2011;134(Pt 5):1438-46.
59. Aarts E, Roelofs A, Franke B, et al. Striatal dopamine mediates the interface between motivational and cognitive control in humans: evidence from genetic imaging. *Neuropsychopharmacology*. Aug 2010;35(9):1943-51.
60. Ahlskog JE. Think before you leap Donepezil reduces falls? *Neurology*. Oct 5 2010;75(14):1226-7.

Part I

Cognitive control of
gait and balance in
patients with chronic stroke

Chapter 2

Community-dwelling people
with chronic stroke need
disproportionate attention while
walking and negotiating obstacles

Katrijn Smulders, Roos van Swigchem, Bert de Swart, Alexander Geurts,
Vivian Weerdesteyn

Gait & Posture 2012; 36(1): 127-32



Abstract

Background: The objective of the present study was to examine the attentional demands of gait adaptations required to walk over irregular terrain in community-dwelling people with chronic stroke.

Methods: Eight community ambulators (>6 months post-stroke, aged 57±15 years) and eight age-matched healthy controls participated in the study. As the primary motor task, participants walked on a treadmill while they quickly reacted to a sudden obstacle in front of the affected (in the stroke group) or left (in healthy controls) leg. The secondary, cognitive task was an auditory Stroop task. Outcomes were avoidance success rate and muscle reaction times of the biceps and rectus femoris (motor task), and a composite score of accuracy and verbal reaction time (cognitive task).

Results: Success rates did not differ between single and dual task conditions in either group, while muscle reaction times deteriorated equally during the dual task in both groups. However, compared with the Stroop scores just before and after obstacle crossing, the scores while crossing the obstacle deteriorated more in the stroke group than in the controls ($p=0.012$).

Conclusion: The higher dual task costs on the Stroop task reflect greater attentional demands during walking and crossing obstacles. The absence of dual task effects on obstacle avoidance performance suggests that the people with stroke used a “posture first strategy”. The results imply that common daily life tasks such as obstacle crossing while walking require disproportionate attention even in well-recovered people with stroke.

Introduction

Following acute stroke, 2 out of 3 patients are unable to walk independently. Although approximately 66% of the patients that could not walk initially regain independent walking ability, a large number of people with chronic stroke continue to experience significant gait deficits.¹ In general, gait deficits result in increased attentional demands in order to maintain stability and prevent stumbling or falling.²

Increased attentional demands of walking can have important consequences, as in daily life we frequently walk over irregular terrain, while simultaneously negotiating obstacles and having a conversation. The common way to assess the attentional demands of walking is to add a secondary cognitive task, and compare the performance between the single and dual task conditions.³ The assumption underlying these dual task paradigms is that the attentional demands of the two tasks combined exceed the total attentional capacity,⁴ demonstrated by deteriorated performance on the primary or secondary task, or on both. Thus, larger decrements in motor and/or cognitive task performance reflect greater attentional demands.

In elderly populations, larger dual task interference in gait tasks is associated with an increased fall risk.⁵⁻⁷ In people with stroke, there is no conclusive evidence yet for increased attentional demands during (complex) walking compared to age-matched healthy controls.⁸⁻¹⁰ This is surprising since even well-recovered people with stroke often complain of the fact that walking over uneven terrain and in complex environments requires full attention in order not to fall.

The absence of conclusive evidence for increased attentional demands of walking in people with stroke may be explained by the methods used. In all prior dual task experiments, the gait task involved walking over even terrain, for instance an institution's hallway. As these situations do not impose a serious threat to balance maintenance, the gait task may be too easy to simulate the challenges of daily life.¹¹ Furthermore, in previous studies,^{10,12,13} the secondary cognitive tasks did not impose major temporal constraints on, for instance, the number of answers to be given within a specific time. As a result, participants may have shifted their attention between the tasks rather than paying attention to both tasks simultaneously. This strategy may have enabled them to operate within the limits of their attentional capacity and maintain adequate performance. Lastly, dual task effects may have remained undetected because the performance on the secondary task was either left out of consideration, or was reported in terms of rather crude outcome measures (e.g. number of errors).⁸⁻¹⁰ To fully capture the dual task interference, it is necessary to precisely measure dual task costs on both the primary and secondary task.

In the present study, we aimed to objectify the attentional demands of gait adaptations required to negotiate irregular or cluttered terrain in people with stroke. To this aim we conducted a dual task experiment in community ambulators able to walk independently over even and uneven surfaces. They had to avoid obstacles during walking while concurrently responding to a secondary, cognitive task. As the cognitive task we used the auditory Stroop paradigm, a time-critical task requiring continuous attention, which has previously been able to elicit dual task costs even in healthy young adults.¹⁴ This methodology enabled us to substantially stress the attentional capacity and minimize the possibility to switch attention between tasks. We hypothesized that people with stroke would demonstrate greater dual task costs during obstacle crossing than healthy subjects.

Methods

Subjects

Eight community ambulators with chronic (>6 months post-onset) stroke (5 men, aged 57±15 years) and eight age- and sex-matched healthy controls (aged 54±15 years) participated in the experiment. More detailed characteristics of the stroke group are presented in Table 1. People with stroke were recruited from a larger sample that had previously participated in a study on the effect of transcutaneous peroneal stimulation.¹⁵ All subjects suffered from a drop foot and regularly used an ankle-foot orthosis. To be included, they had to be able to walk independently without walking aid for more than 10 minutes on all surfaces (Functional Ambulation Categories 5),¹⁶ and had to have a score ≥50 on the Berg Balance Scale.¹⁷ Exclusion criteria were a range of ankle motion <30 degrees, inability to load the heel while standing with an extended knee, severe hypertonia of the calf (Modified Ashworth Scale scores 4 and 5) at the affected body side, or any impairment that could interfere with the ability to carry out the cognitive task, e.g. aphasia. The regional medical ethical committee approved the experimental protocol and all subjects gave their written informed consent.

Obstacle avoidance task

During the obstacle avoidance task participants walked on a treadmill while wearing their own comfortable low-heeled shoes, at a constant velocity of 2 or 3 km/h, dependent on the walking abilities of the stroke subjects.¹⁸ The velocity of healthy subjects was matched to the velocity of the stroke subjects. For safety reasons, all subjects wore a harness attached to a ceiling-mounted rail. A wooden obstacle (40x30x1.5 cm) was placed under a bridge just above the treadmill in

front of the affected (in the stroke group) or left (in controls) leg of the subjects (Fig 1b).

Three reflective markers were placed on the heel, the hallux and lateral malleolus of each foot. Using a 6-camera 3D motion analysis system (Vicon), movement of the feet was recorded (sample frequency 100Hz). These signals were processed online in order to detect heel strikes. Based on this information, the computer triggered the obstacle to be released at different, pre-set phases of the step cycle. As a consequence, the instant of obstacle release was unexpected. Participants were instructed to cross the obstacle without touching it or placing the crossing foot beside the obstacle. Failures in obstacle crossing were noted and checked after the measurement using video recordings.

Muscle activation of the biceps femoris of the crossing leg and the rectus femoris of the contralateral (supporting) leg were recorded, because the first responses to the obstacle are observed in these muscles.^{19,20} Electromyography (EMG) electrodes were placed on the bellies of the muscles according to SENIAM guidelines (sample frequency 1000 Hz).

Table 1: Characteristics of the stroke group

Subject	Age (yrs)	Gender	Time post-stroke (months)	Type of lesion	Side of lesion	MI (0-100)	FMI (% FR)	BBS (0-56)
P1	69	M	49	Infarction	Left	64	75	54
P2	71	M	133	Infarction	Right	64	86	55
P3	60	M	42	Infarction	Right	57	64	50
P4	56	M	21	Infarction	Right	72	71	55
P5	55	F	87	Infarction	Right	72	75	53
P6	60	M	13	Infarction	Left	64	71	55
P7	61	F	98	Infarction	Left	64	61	53
P8	22	F	97	Hemorrhage	Right	64	79	55

MI = Motricity Index, FMI = Fugl-Meyer Index, FR = Functional recovery, BBS = Berg Balance Scale

Auditory Stroop task

We chose the auditory Stroop task as the secondary, cognitive task.²¹ In this task, subjects listened to the words “high” or “low” spoken at a high or low pitch, presented through headphones (Sennheiser) with an interstimulus-interval of 2 sec. Subjects were instructed to respond as fast as possible by verbally indicating the pitch of the stimulus. For instance, the word “high” was presented at a high (congruent, correct response is ‘high’) or a low pitch (incongruent,

correct response is 'low'), which introduced two difficulty levels depending on congruency.

Stroop stimulus signals were recorded at a sample frequency of 1000 Hz. Responses of the subjects were recorded by the microphone attached to the headphone at the same sample frequency (1000 Hz). Accuracy of the verbal responses was checked after the experiment using the video camera.

Procedure

Each measurement started with 20 Stroop stimuli to practice the task. Subsequently, the subjects performed a series of 40 Stroop stimuli while seated (seated Stroop). Then, all subjects familiarized with treadmill walking followed by 1.5 minutes of unperturbed walking with a concurrent Stroop task (dual task unperturbed walking). Subsequently, subjects performed 5 familiarization trials of the obstacle avoidance task. Thereafter, 18 obstacle trials were collected without the Stroop task (single task obstacle avoidance), and 18 trials while responding simultaneously to the Stroop task (dual task obstacle avoidance). Participants were instructed to keep up the performance of both tasks during the dual task conditions.

To eliminate possible sequence effects, half of the group started the avoidance trials in the single task condition, whereas the other half started the avoidance trials in the dual task condition.

Data analysis

Obstacle avoidance trials were analyzed with regard to the time available to respond to the obstacle.¹⁴ Trials in which the available reaction time was too short (<150 ms) or too long (>600 ms) were excluded for all further analyses.

For each participant, avoidance success rates for the single and dual task conditions were calculated as the number of successful trials divided by the total number of trials. With regard to the EMG data, signals were band-pass filtered (4th order butterworth, 20-450 Hz), rectified and subsequently low-pass filtered at 25 Hz. Mean EMG activity during unperturbed walking was calculated for rectus and biceps femoris from the strides preceding the obstacle release (reference strides). Muscle onset latencies were defined as the instant at which the EMG signal of the crossing stride deviated more than two standard deviations from the reference strides. Onsets were detected for all trials (failed and successful trials) by a computer algorithm and confirmed by visual inspection.

The stimulus and response signals of the Stroop task were rectified and low-pass filtered at 40 Hz. Onsets of the stimuli and the responses were visually inspected. Verbal reaction times were calculated by subtracting the onset of the

stimulus from the onset of the response. To account for a speed-accuracy trade-off,²² verbal reaction time and accuracy were combined in a composite score (Eq. 1).²³

Equation 1:

$$\text{Composite score} = \frac{\text{Accuracy (\%)}}{\text{Verbal reaction time (s)}}$$

Statistical analysis

For each participant, 5 composite scores on the Stroop task were calculated. The first composite score was calculated as the mean score over the 40 responses during the seated Stroop task, and the second composite score as the mean over all responses during dual task unperturbed walking (Fig. 1A). The third to fifth Stroop composite scores were retrieved from the dual task obstacle avoidance condition and were computed as the mean scores over 18 trials. The third composite score was obtained from the pre-obstacle response, defined as the response to the last Stroop stimulus before the obstacle was released (Fig. 1B). The fourth composite score was computed for the obstacle crossing response, defined as the response to the first Stroop stimulus after obstacle release (Fig. 1C). The fifth composite score was obtained from the response to the subsequent Stroop stimulus (i.e. post-obstacle response; Fig 1D).

The effect of the addition of a secondary cognitive task on the avoidance success rate was analyzed using a 2x2 (group x task) repeated measures (RM-) ANOVA. To evaluate the effect of dual tasking on BF and RF reaction times, we conducted a 2x2x2 (group x task x muscle) RM-ANOVA. The effects of dual tasking on the Stroop performance were tested in a 2x4x2 (group x response x congruency) RM-ANOVA. The four response conditions that were distinguished were unperturbed walking, pre-obstacle, obstacle crossing and post-obstacle trials. Post-hoc analyses were used for pair-wise comparisons when significant main effects were found and simple contrasts when interaction effects were found. Finally, to test whether seated Stroop composite scores differed from Stroop scores during unperturbed walking, a 2x2x2 (group x task x congruency) RM-ANOVA was conducted. For all main analyses, significance was accepted at $p < 0.05$. For post-hoc comparisons, significance was accepted at $p < 0.01$.

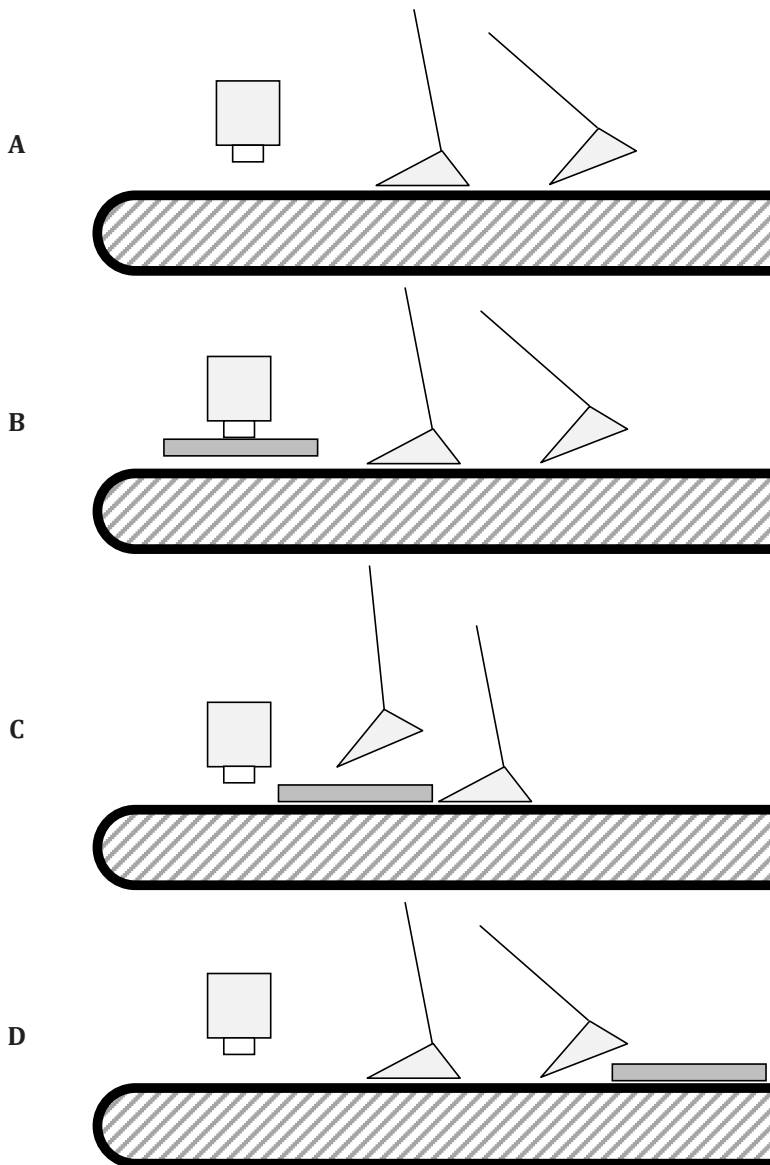


Figure 1. Schematic illustration of the four dual task conditions. **A.** Unperturbed walking: The subject responded to the Stroop stimuli while walking on the treadmill without an obstacle present. **B.** Pre-obstacle trial: The obstacle was placed in front of the subject and was about to fall. The pre-obstacle response was the response to the last Stroop stimulus before the obstacle was released. **C.** Obstacle crossing: Release of the obstacle on the treadmill. The obstacle response was defined as the response to the first Stroop stimulus after obstacle release. **D.** Post-obstacle trial: The subject has just crossed the obstacle. The post-obstacle Stroop response was the response to the second Stroop stimulus after obstacle release.

Results

Dual task effects on obstacle avoidance

There was no significant interaction effect of group x task ($F_{1,14}=2.419, p=0.142$), nor a main effect of task on the avoidance success rate ($F_{1,14}=2.419, p=0.142$), indicating that the addition of the Stroop task did not lead to more failures in either of the two groups (Fig. 2). Further, a significant main effect of group indicated that the stroke group was generally less successful ($53\pm33\%$) in avoiding obstacles than the healthy subjects ($99\pm1\%$, $F_{1,14}=15.42, p=0.002$).

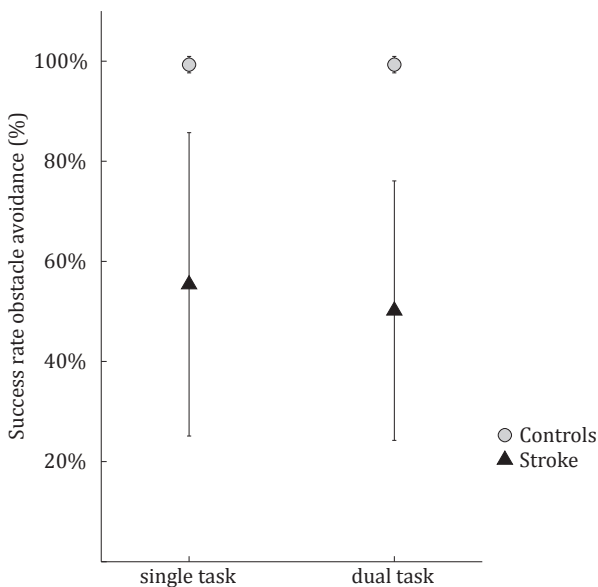


Figure 2. Means and 95% CI of avoidance success rates of the stroke group (black triangles) and the healthy subjects (grey circles).

Regarding the onset latencies of the muscles, there was no significant interaction effect of group x task ($F_{1,14}=0.50, p=0.490$), indicating that in the dual task condition the stroke group did not deteriorate more than the healthy subjects (Fig. 3). A significant main effect of task ($F_{1,14}=16.79, p=0.001$) indicated that the addition of the Stroop task resulted in delayed muscle onsets (19 ms in biceps femoris and 21 ms in rectus femoris). Furthermore, there was a main effect of group ($F_{1,14}=8.19, p=0.013$, Fig. 3) showing 36 ms later onsets of biceps femoris and 26 ms later onsets of rectus femoris activity for subjects with stroke compared to healthy subjects. No significant main or interaction effects of the factor muscle were identified (all $p's \geq 0.174$).

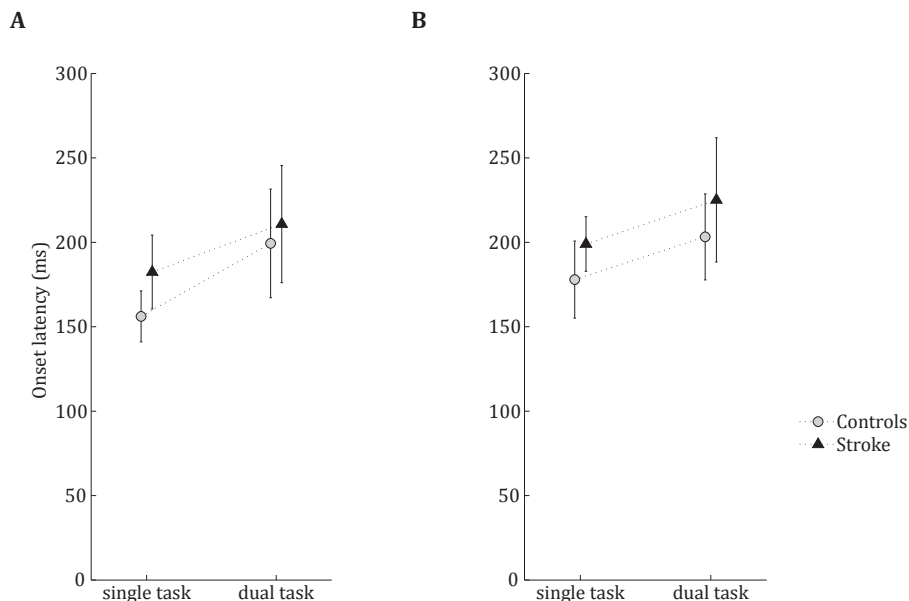


Figure 3. Onset latencies (means and 95% CI) of biceps femoris of the crossing leg (left panel) and rectus femoris of the contralateral (supporting) leg (right panel) for the stroke group (black triangles) and healthy controls (grey circles) in both single and dual task conditions. **A.** Biceps femoris of crossing leg, **B.** Rectus femoris of contralateral leg

Dual task effects on the cognitive task

There was a significant group \times response condition interaction effect ($F_{3,14}=4.11$, $p=0.012$, Fig. 4) on the Stroop composite scores. Post-hoc analysis showed that this interaction was restricted to the comparison between pre-obstacle and obstacle crossing responses ($F_{1,14}=10.42$, $p=0.006$) and between obstacle crossing and post-obstacle responses ($F_{1,14}=11.75$, $p=0.004$). Subjects with stroke lost 35% on the obstacle crossing responses compared to the pre-obstacle responses, whereas controls lost 17%.

Analysis of the seated Stroop performance compared to unperturbed walking did not yield a significant interaction effect of group \times task ($F_{1,14}=0.363$, $p=0.556$), nor a significant main effect of group ($F_{1,14}=0.127$, $p=0.727$). There was a main effect of congruency ($F_{1,14}=27.04$, $p<0.001$), with lower composite scores for incongruent compared to congruent Stroop stimuli, but there were no significant interaction effects with congruency (all $p\geq 0.382$).

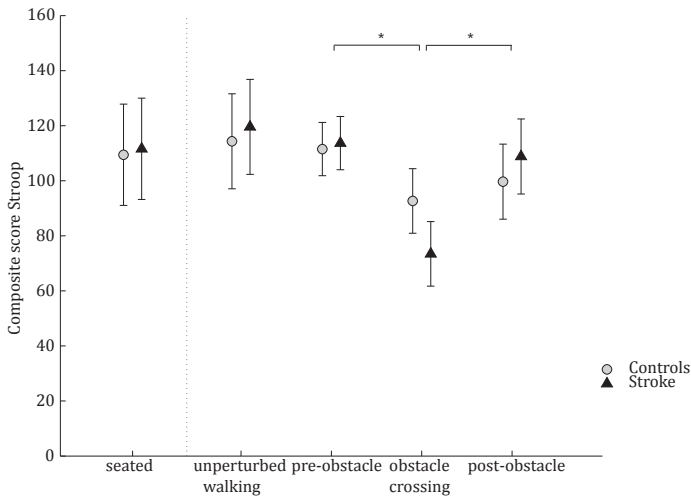


Figure 4. Composite scores (means with 95% CI) on the Stroop task for the stroke group (black triangles) and healthy controls (grey circles) for the five task conditions.

* Significant group x response interaction effects ($p < 0.01$).

Discussion

This study examined the effect of a secondary cognitive task on the ability to avoid obstacles while walking on a treadmill in well-recovered people with chronic stroke. Whereas the subjects with stroke were less successful than controls in negotiating obstacles, and although they demonstrated delayed muscle responses in both the crossing and supporting leg, the addition of the Stroop task did not affect their obstacle avoidance performance or muscle response times more than in controls. Yet, the stroke group showed considerably greater loss on the cognitive task performance during obstacle crossing.

These results indicate that the subjects with stroke prioritized the obstacle crossing task over the Stroop task, despite the instruction to keep up their performance of both tasks. This seems to be an appropriate choice, often referred to as the 'posture first' strategy.³ In daily life, prioritizing balance over other (less essential) tasks is usually the safest option. The clinical relevance of the posture first strategy is illustrated by the findings by Siu et al.²⁴ who reported that older adults with a history of falling experienced difficulties with prioritizing gait in dual task situations.

Interestingly, like the control subjects, the subjects with stroke did not deteriorate their Stroop task performance during unperturbed walking, pre-obstacle and post-obstacle trials compared to sitting. This indicates the specificity of the observed dual task interference, which is restricted to the very instant of

obstacle crossing. Because the walking speed was fixed, participants could not apply a strategy of reducing their gait velocity to deal with the dual task demands, which was the most consistent finding in previous studies.² It may be that in dual task walking at a preferred speed, changes in gait velocity reflect what people would *naturally* do opposed to what they are *capable* of. The presently applied paradigm with a fixed gait speed most likely forced participants to exploit their maximum capacity. Hence, the presence of dual task effects on the Stroop task *only during* obstacle crossing suggests that well-recovered people with stroke may not have major difficulties walking over even terrain while being engaged in an attention-demanding secondary task, but that they do experience problems during dual task walking over irregular terrain which requires gait adaptations.

The absence of increased dual task effects on the motor task in people with stroke is in line with the results of Canning et al.,⁸ who did not find differential dual task effects on gait speed or stride length between a stroke group and healthy controls. On the other hand, Haggard and co-workers⁹ demonstrated that people with stroke adjusted their stride time significantly more than healthy subjects when concurrently responding to a cognitive task. Hyndman et al.¹⁰ also observed increased dual task effects of stroke, however only on walking time, not on stride length. Possibly, the type of cognitive task used, and consequently the attentional demands of the task, can account for these inconsistent results.

A limitation of our study was the homogeneity of the stroke sample, all community ambulators, which limits generalization to a more severely affected stroke population. Nevertheless, in this well-recovered stroke group, decrements in dual task performance could be demonstrated for a task that simulates obstacle avoidance during complex walking conditions encountered in daily life. Such decrements may even be greater in people with more pronounced balance and gait deficits. This remains to be investigated in future studies. Another limitation was that the small sample size of our study could have resulted in false negative findings. However, the means of the groups were close together when not-significant, not exceeding 5%. Still, if a larger sample size would have yielded significant differences between groups, their clinical relevance would be questionable. Finally, we did not assess the cognitive status of the participants as a possible confounder in dual tasking. More specifically, (prefrontal) executive functions have been proposed to be involved in allocating attention to different tasks at the same time.² Indeed, in people with Parkinson's disease²⁵ and in Alzheimer's disease,²⁶ executive deficits are associated with decrements in dual task performance. It seems unlikely, however, that our participants suffered from such executive deficits, because their performance on the Stroop task, a well-established measure of executive functioning, was as good as in the healthy

controls both while sitting and unperturbed walking.

Our results demonstrate that well-recovered people with stroke need a disproportionate amount of attention while walking and negotiating obstacles as a common task in everyday life. Yet, the extra attentional costs could be elicited *only during* obstacle crossing as opposed to unperturbed walking and pre- and post-obstacle trials. It may be that this increased dual task interference makes people with stroke vulnerable to situations in which their gait is challenged and concurrent tasks demand attention at the same time. Future studies are necessary to further substantiate this notion and to relate dual task performance to fall risk after stroke.

References

1. Jorgensen L, Engstad T, Jacobsen BK. Higher incidence of falls in long-term stroke survivors than in population controls: depressive symptoms predict falls after stroke. *Stroke*. 2002;33(2):542-7.
2. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329-42.
3. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture*. 2002;16(1):1-14.
4. Kahneman D. Attention and task interference. In: Kahneman D, ed. *Attention and Effort*. Englewood-Cliffs, New Jersey: Prentice-Hall; 1973:178-201.
5. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? *Eur J Neurol*. Jul 2009;16(7):786-95.
6. Faulkner KA, Redfern MS, Cauley JA, et al. Multitasking: association between poorer performance and a history of recurrent falls. *J Am Geriatr Soc*. 2007;55(4):570-6.
7. Verghese J, Buschke H, Viola L, et al. Validity of divided attention tasks in predicting falls in older individuals: a preliminary study. *J Am Geriatr Soc*. 2002;50(9):1572-6.
8. Canning CG, Ada L, Paul SS. Is automaticity of walking regained after stroke? *Disabil Rehabil*. 2006;28(2):97-102.
9. Haggard P, Cockburn J, Cock J, Fordham C, Wade D. Interference between gait and cognitive tasks in a rehabilitating neurological population. *J Neurol Neurosurg Psychiatry*. 2000;69(4):479-86.
10. Hyndman D, Ashburn A, Yardley L, Stack E. Interference between balance, gait and cognitive task performance among people with stroke living in the community. *Disabil Rehabil*. 2006;28(13-14):849-56.
11. Lord SE, Rochester L. Measurement of community ambulation after stroke: current status and future developments. *Stroke*. 2005;36(7):1457-61.
12. Cockburn J, Haggard P, Cock J, Fordham C. Changing patterns of cognitive-motor interference (CMI) over time during recovery from stroke. *Clin Rehabil*. 2003;17(2):167-73.
13. Lord SE, Rochester L, Weatherall M, McPherson KM, McNaughton HK. The effect of environment and task on gait parameters after stroke: A randomized comparison of measurement conditions. *Arch Phys Med Rehabil*. 2006;87(7):967-73.
14. Weerdesteyn V, Schillings AM, van Galen GP, Duysens J. Distraction affects the performance of obstacle avoidance during walking. *J Mot Behav*. 2003;35(1):53-63.
15. Van Swigchem R, Vloothuis J, Den Boer J, Weerdesteyn V, Geurts AC. Is transcutaneous peroneal stimulation beneficial to patients with chronic stroke using an ankle-foot orthosis? A within-subjects study of patients' satisfaction, walking speed and physical activity level. *J Rehabil Med*. 2010;42(2):117-21.
16. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. *Int Disabil Stud*. 1990;12(1):6-9.
17. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review. *Phys Ther*. 2008;88(5):559-66.
18. Weerdesteyn V, Nienhuis B, Hampsink B, Duysens J. Gait adjustments in response to

- an obstacle are faster than voluntary reactions. *Hum Mov Sci.* 2004;23(3-4):351-63.
19. Hofstad CJ, Weerdesteyn V, van der LH, Nienhuis B, Geurts AC, Duysens J. Evidence for bilaterally delayed and decreased obstacle avoidance responses while walking with a lower limb prosthesis. *Clin Neurophysiol.* 2009;120(5):1009-15.
 20. Weerdesteyn V, Nienhuis B, Geurts AC, Duysens J. Age-related deficits in early response characteristics of obstacle avoidance under time pressure. *J Gerontol A Biol Sci Med Sci.* 2007;62(9):1042-7.
 21. Cohen G, Martin M. Hemisphere differences in an auditory Stroop test. *Percept Psychophys.* 1975;17(1):79-83.
 22. Wickelgren WA. Speed-accuracy tradeoff and information processing dynamics. *Acta Psychologica.* 1977;41(1):67-85.
 23. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950-7.
 24. Siu KC, Lugade V, Chou LS, van DP, Woollacott MH. Dual-task interference during obstacle clearance in healthy and balance-impaired older adults. *Aging ClinExpRes.* 2008;20(4):349-54.
 25. Lord S, Rochester L, Hetherington V, Allcock LM, Burn D. Executive dysfunction and attention contribute to gait interference in ,off' state Parkinson's Disease. *Gait Posture.* 2010;31(2):169-74.
 26. Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. *J Am Geriatr Soc.* 2003;51(11):1633-7.

Chapter 3

Evaluating the concept of gait adaptability training for improving gait adjustments and associated attentional demands after stroke

Mariëlle van Ooijen, Anita Heeren, Katrijn Smulders, Alexander Geurts,
Thomas Janssen, Peter Beek, Vivian Weerdesteyn, Melvyn Roerdink

Submitted



Abstract

Background: To evaluate the concept of gait adaptability training with an innovative rehabilitation treadmill augmented with visual context (e.g., obstacles, stepping targets) for improving step adjustments and associated attentional demands during walking.

Methods: Sixteen community-ambulating persons in the chronic stage after stroke (age: 54.8 ± 10.8 yrs; time post stroke: 1.4 ± 0.9 yrs) participated in this observational study with pretest-posttest design. Participants received ten sessions of C-Mill gait adaptability training within 5-6 weeks. Prior to and after the intervention, participants performed an obstacle avoidance task with and without a secondary attention-demanding auditory Stroop task to examine their ability to make step adjustments during walking (i.e., obstacle avoidance success rates) as well as associated attentional demands (i.e., Stroop success rates, stratified for pre-crossing, crossing, and post-crossing strides).

Results: Obstacle avoidance success rates improved after C-Mill training from $52.4\% \pm 16.3\%$ at pretest to $77.0\% \pm 16.4\%$ at posttest ($p < 0.001$). This improvement was accompanied by greater Stroop success rates during the obstacle-crossing stride (pretest: $62.9\% \pm 24.9\%$, posttest: $77.5\% \pm 20.4\%$, $p = 0.006$).

Conclusion: C-Mill training may improve the ability to make step adjustments during walking and lower the associated attentional demands after stroke. The study provides support and guidance for conducting a randomized controlled trial to confirm the potential of C-Mill training for improving safe community ambulation after stroke.

Introduction

Stroke is a worldwide health problem and a leading cause of serious long-term adult disability.¹ Although the vast majority of stroke survivors regain independent walking capacity,^{2,3} walking after stroke is often impeded by persistent balance and gait deficits, and even well-recovered people in the chronic stage after stroke have an elevated fall risk.^{4,5}

Safe and independent ambulation requires the ability to make step adjustments relative to environmental demands, such as when walking over cluttered terrain or when avoiding obstacles. Previous research has shown that this important aspect of walking (termed 'gait adaptability')^{6,7} is impaired after stroke.^{6,8-11} Like walking in older adults, walking after stroke may also require more attention.¹²⁻¹⁴ The attentional demands of walking increase even further when gait adjustments are required,¹⁰ limiting the processing of concurrent cognitive information, such as attending to traffic lights or potential trip hazards. Evidently, an impaired ability to make gait adjustments along with increased attentional demands hampers safe community ambulation. Hence, there is a clear need to improve gait adaptability in community-ambulating people after stroke.

Specifically for the practice of gait adaptability, a rehabilitation treadmill augmented with visual context was recently developed.¹⁵ This so-called C-Mill (ForceLink, Culemborg, the Netherlands) allows for intensive practice of foot positioning relative to visual objects (e.g., obstacles and stepping targets) projected on the walking surface (Figure 1). This projected visual context evokes step adjustments, mimicking the task-specific gait adjustments required for safe community ambulation. The development of the C-Mill was incited by recommendations for task-specific exercise programs after stroke,^{16,17} and more specifically, for incorporating the complex and hazardous situations of everyday walking in gait training programs.⁴ In fact, promising initial results of gait adaptability training have been reported in different populations prone to falling, for example in older adults after overground gait adaptability training^{18,19} and in persons with Parkinson's disease and stroke after treadmill-based virtual-reality gait adaptability training.²⁰⁻²² These studies reported improvements in the ability to make step adjustments during walking (i.e., obstacle avoidance)¹⁸⁻²² and lower fall incidence.^{18,19} To date, however, it is unknown whether gait adaptability training also improves the attentional demands of adaptive walking, which is unfortunate in view of its importance for safe community walking.

Before conducting a multicentre randomized controlled trial, novel rehabilitation interventions should ideally go through a progression of pilot studies to first establish its safety, feasibility, and potential to improve relevant

outcome measures.²³ Heeren et al.²⁴ already showed that C-Mill gait adaptability training is a feasible, well tolerated and appreciated form of gait training after stroke, with the potential to improve balance, gait, physical activity, and accuracy of step adjustments during stance. The purpose of the present pilot study was to evaluate the concept of C-Mill training for improving step adjustments during walking and associated attentional demands in a group of persons in the chronic stage after stroke. To quantify these two important determinants of safe community walking, the frequently used Nijmegen obstacle avoidance paradigm was used before and after ten sessions of C-Mill training as a laboratory assessment of gait adaptability.^{11,25,26} To assess the attentional demands of step adjustments during walking, this paradigm was conducted with and without performing a secondary, attention-demanding auditory Stroop task (cf. Smulders et al.).^{10,27} After C-Mill training, improved obstacle avoidance success rates at lower attentional costs were expected.

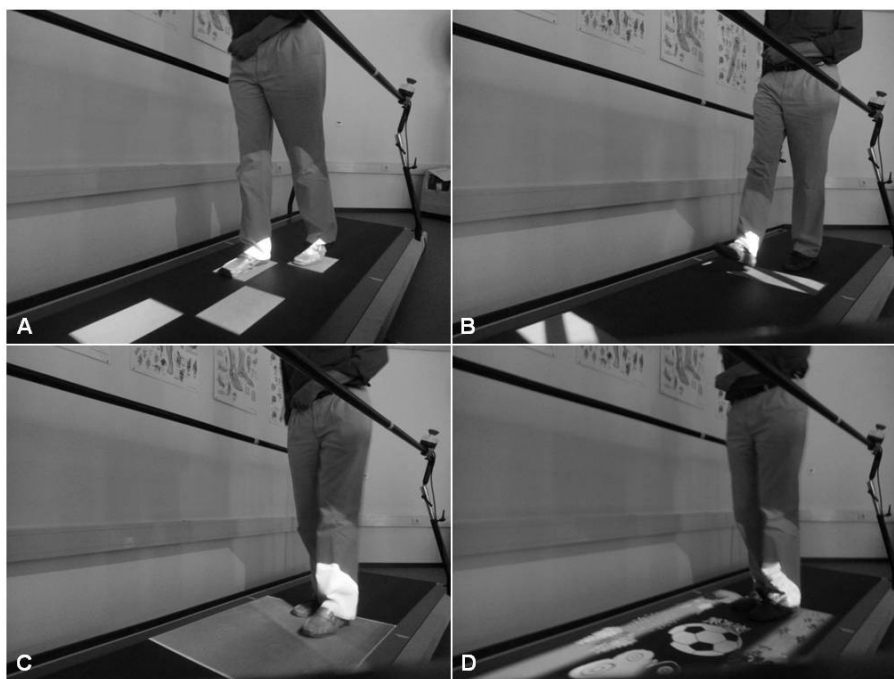


Figure 1. The C-Mill is a 3-m long instrumented treadmill augmented with visual objects, such as stepping targets and obstacles, projected on the belt to facilitate practicing foot positioning relative to environmental context. **A.** Visually guided stepping to a sequence of irregularly spaced stepping targets, **B.** obstacle avoidance, **C.** speeding up and slowing down by maintaining position in an anteriorly-posteriorly moving walking zone, and **D.** all of the above in a functional and interactive gait adaptability game.

Methods

Participants

Participants of this study took part in a previous study in which safety, feasibility and balance- and gait-related benefits of C-Mill training were evaluated.²⁴ Sixteen community-ambulating persons in the chronic stage after stroke were included. They were all referred for gait adaptability training in an outpatient rehabilitation program in Amsterdam or Nijmegen, the Netherlands between January and September 2011. To be included in the study, participants had to be more than six months after their first unilateral supratentorial stroke and be able to walk independently (Functional Ambulation Categories 4-5)²⁸ at a speed of at least 2 km/h. Exclusion criteria were other disorders that influence walking, serious cognitive impairments resulting in insufficient comprehension, severe visual deficits limiting the correct perception of the direct environment, and the use of psychotropic medication.

Participant characteristics were assessed by a rehabilitation physician during an intake visit. Participant characteristics, including lower-limb muscle strength (Motricity Index),²⁹ motor selectivity (Fugl-Meyer Assessment),³⁰ and vibration sense (Rydel-Seiffer tuning fork,³¹ Arno Barthelmes & Co, Tuttlingen, Germany) as well as walking speed (10 m walk test)³² and the presence of visual field deficits and visual spatial hemineglect (i.e., the presence of visual extinction) as assessed with confrontation visual field exams are presented in Table 1. All participants gave written informed consent and the study was approved by the regional medical ethics committee.

C-Mill training intervention

Participants received ten sessions of 1-hour C-Mill training over a period of 5-6 weeks (two sessions per week) from an experienced physical therapist. C-Mill training sessions (Figure 1) included six blocks of predefined gait adaptability exercises of which difficulty was increased progressively over time to ensure that the training remained sufficiently challenging throughout the intervention program. Content and duration of gait adaptability exercises were described previously²⁴ and are summarized in Table 2.

Table 1. Demographic and clinical characteristics of participants (n=16)

Subject	Age (yrs)	Gender	Time post- stroke (yrs)	Paretic side	FAC	MI (0-100) *†	FMA (%) *†	10MWT (s)	Vibration sensation threshold (0-8) †	Visuospatial hemineglect	Visual field deficit
1	47.0	Male	3.2	Left	5	84	82	10.6	MM: 2.0, IJH: 3.5	Delayed	Not present
2	52.3	Male	2.4	Left	5	78	65	10.4	MM: 5.5, IJH: 6.0	Normal	Not present
3‡	60.8	Male	1.6	Right	5	78	76	9.3	MM: 6.0, IJH: 4.0	Normal	Not present
4	60.6	Female	1.8	Left	5	92	82	8.1	MM: 4.5, IJH: 3.0	Delayed	Not present
5	58.8	Male	1.2	Left	5	64	76	8.5	MM: 2.0, IJH: 2.5	Normal	Not present
6	45.6	Female	0.7	Left	5	57	74	10.9	MM: 6.5, IJH: 5.5	Normal	Not present
7	56.4	Female	3.3	Left	5	78	79	12.3	MM: 6.0, IJH: 4.5	Normal	Not present
8	47.3	Male	0.8	Right	5	68	68	7.3	MM: 3.0, IJH: 1.5	Normal	Not present
9	50.1	Female	0.5	Left	4	80	71	13.1	MM: 7.5, IJH: 7.5	Normal	Not present
10	68.4	Male	0.9	Right	4	100	79	8.9	MM: -, IJH: -	Normal	Not present
11	69.0	Male	1.2	Right	5	85	88	8.4	MM: 4.0, IJH: 7.5	Normal	Not present
12	69.8	Female	1.0	Left	5	78	91	10.0	MM: 2.5, IJH: 2.5	-	Present
13	38.5	Female	1.6	Right	5	78	85	9.6	MM: 6.0, IJH: 7.0	Normal	Not present
14	38.8	Female	1.3	Right	5	85	94	9.0	MM: 6.5, IJH: 6.5	Normal	Not present
15	44.7	Male	0.9	Left	5	100	74	7.0	MM: 5.0, IJH: 5.0	Normal	Not present
16	68.3	Male	0.7	Right	5	92	100	9.1	MM: 4.0, IJH: 4.0	Normal	Not present
Mean	54.8	9 Male 7 Female	1.4	7 Right 9 Left (median)	5	81	80	9.5	MM: 5.0 (median) IJH: 5.5 (median)	13 Normal 2 Delayed	15 Not present 1 Present
SD	10.8		0.9	4-5 (range)		11	10	1.7	MM: 2.0-7.5 (range) IJH: 1.5-7.5 (range)		

FAC, Functional Ambulation Categories; MI, Motricity Index; FMA, Fugl-Meyer Assessment; 10MWT, 10 Meter Walk Test; MM, Medial malleolus; IJH, Interphalangeal joint hallux. *Scores of lower extremity, †Scores of paretic side, ‡ Participant with drew from the study

Table 2. C-Mill training intervention.

Block	Gait adaptability exercises	Duration (min)
1	Warm-up period: regular walking without projected visual context.	5
2	Visually guided stepping: practice of foot positioning relative to a projected sequence of irregularly spaced stepping targets, which could be made more challenging by increasing the degree of irregularity in the sequence of targets. Moreover, targets could unexpectedly change to obstacles, which introduced cognitive decision-making and required online step adjustments. (Fig. 1A)	7
3	Obstacle avoidance: practice of obstacle avoidance by projecting visual obstacles on the belt's surface. Difficulty could be manipulated by changing the size of the projected obstacles and the time available to respond to the obstacles. (Fig. 1B)	7
4	Speeding-up and slowing-down: practice of speed-related gait adjustments by projecting a walking area of approximately 1 m ² that moved over the treadmill surface in anterior-posterior direction. Participants had to accelerate and decelerate relative to the constant belt speed to stay in the moving walking area, which could accelerate to different extents to alter the level of difficulty and predictability. (Fig. 1C)	7
5	Tight-rope walking: practice of visually guided stepping exercises that required walking with a narrow base of support.	7
6	Fun and functional game: participants could score points by hitting the interactive targets (e.g., footballs), but also lose points when they accidentally landed on an obstacle (e.g., sheep, fences). (Fig. 1D)	7

Training sessions consisted of six blocks of gait adaptability exercises, starting with the warm-up period (block 1) and ending with the fun and functional game (block 6). All other blocks were performed in random order from session to session

Procedure

In the week prior to the intervention period (pretest) and in the week after the intervention period (posttest), participants performed the treadmill-based obstacle avoidance task under single and dual task conditions (i.e., with and without a secondary attention-demanding auditory Stroop task). Participants were acquainted with these tasks during a familiarization session at the intake visit in the week prior to pretest.

Pretest and posttest assessments started with one minute of practicing the auditory Stroop task while seated (i.e., approximately 23 Stroop stimuli). Subsequently, participants practiced treadmill walking and performed six practice obstacle avoidance trials. Thereafter, participants performed 30 obstacle avoidance trials, both with and without the auditory Stroop task. In addition, participants performed the auditory Stroop task for one minute in a seated position and while walking on the treadmill without obstacles being present. All tasks were performed in random order to eliminate sequence effects. With regard to the dual task conditions, participants were instructed to perform the obstacle avoidance and Stroop tasks as well as possible.

Obstacle avoidance task

Participants performed the standardized Nijmegen obstacle avoidance task while walking on a treadmill (Figure 2) at either 2 or 3 km/h,^{10,25,26,33,34} depending on their walking ability. At the front of this treadmill, a wooden obstacle (length: 40 cm; width: 30 cm; height: 1.5 cm) was held by an electromagnet above the treadmill surface in front of the participant's affected leg. To register the movement of the feet, reflective markers were placed on the heel, hallux and lateral malleolus of each foot, which were recorded by a 6-camera 3D motion registration system (Vicon, Oxford, UK) at 100 Hz. Marker data were processed in real time to detect heel strike, which was used to trigger obstacle release at different pre-defined but unexpected moments in the gait cycle such that participants had to adjust their gait for a successful avoidance maneuver. Participants wore their own comfortable shoes and orthosis when needed. For safety reasons, participants wore an unobtrusive harness, which was attached to a ceiling-mounted rail.

Participants were instructed to step over the obstacle without touching it and were informed that placing the crossing foot beside the obstacle or holding the handrail was regarded a failure. Failures in obstacle avoidance were registered by an online observer and all obstacle crossings were checked and classified as 'successful' or 'unsuccessful' afterwards using video recordings. In case of doubt, three observers assessed the obstacle crossing to obtain a final classification. Subsequently, individual obstacle avoidance success rates were calculated as

the percentage of successfully avoided obstacles. Trials were excluded from the analysis when obstacle release was not at the predefined moment, when no gait adjustments were required for successful avoidance or when technical malfunctioning precluded video registration (14.0% of the trials).

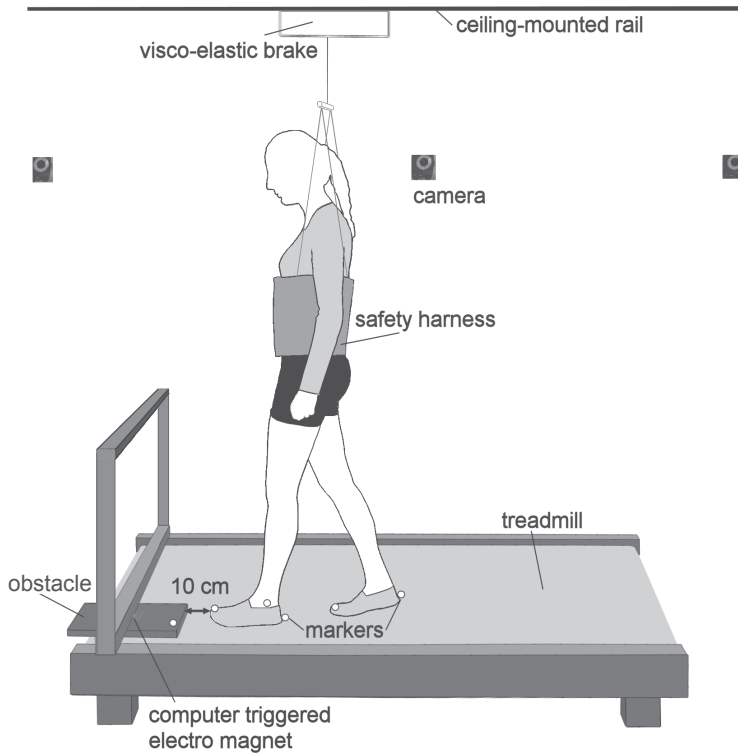


Figure 2. Experimental set-up of the obstacle avoidance task (adapted from Van Swigchem et al. ³³).

Auditory Stroop task

The auditory Stroop task is an attention-demanding task in which the words “high” and “low” are spoken at high and low pitch in random order. The pitch and meaning of the word could therefore be either congruent or incongruent. The words were presented through headphones (Sennheiser, Wedemark, Germany) with an inter-stimulus interval of 2 s, and participants had to report the pitch of the stimulus out loud. Stroop responses were recorded by a microphone attached to the headphone and both Stroop stimuli and responses were sampled with Vicon software (Vicon, Oxford, UK) at 1000 Hz. Moreover, correctness of

verbal responses was registered by an online observer or recorded on video for offline assessment.

Stroop success rates during sitting, unobstructed walking and obstacle avoidance trials were quantified as the percentage of correct Stroop responses. Stroop success rates during obstacle avoidance were stratified relative to the instant of obstacle release (i.e., prior to obstacle crossing [pre-obstacle: defined as the last stimulus-response pair prior to obstacle release], during obstacle crossing [obstacle crossing: the subsequent stimulus-response pair] and after obstacle crossing [post-obstacle: the subsequent stimulus-response pair]). Stroop stimuli were excluded from further analysis when the participant was clearly distracted by a factor other than the Stroop stimulus or when the response was inaudible due to mumbling (3.0% of the stimuli).

Statistical analysis

Obstacle avoidance success rates were compared between pretest and posttest and between single task and dual task conditions with a 2×2 repeated-measures ANOVA (Time \times Task). Stroop success rates were compared between pretest and posttest and among instants of Stroop stimulus presentation (pre-obstacle, obstacle crossing, post-obstacle) using a 2×3 repeated-measures ANOVA (Time \times Instant). Post-hoc analyses were performed using paired-samples *t*-tests.

To control for potential learning effects on the auditory Stroop task, Stroop success rates during sitting and unobstructed walking were tested nonparametrically for main effects of Time (pretest, posttest) and Condition (sitting, unobstructed walking) with a Wilcoxon signed-ranks test. A possible interaction between Time and Condition was analyzed with a Wilcoxon signed-ranks test using the difference values between pretest and posttest of sitting and unobstructed walking.

All statistical analyses were performed using SPSS 20 (SPSS Inc, IBM Corporation, New York, USA). Significance was accepted at $p < 0.05$ for the primary analyses, with a significance level of $p < 0.01$ for post-hoc tests. Effect sizes are presented as partial eta squared (the proportion of variance that a factor explains that is not explained by other factors in the analysis [η^2_p]) for repeated-measures ANOVAs and as *r* for Wilcoxon signed-ranks tests and paired-samples *t*-tests.³⁵ Results are reported as means \pm standard deviations or mean pretest-posttest differences (95% confidence intervals [CI]).

Results

Fifteen participants completed the intervention program, whereas one

participant withdrew from the study after three training sessions because of aggravated lumbago. Three participants reported muscle soreness after the first C-Mill training sessions. No other adverse events were reported. The average time spent walking on the treadmill during training sessions was 38.8 ± 5.2 minutes at an average speed of 2.7 ± 0.4 km/h. Both walking duration and walking speed increased significantly from the first (34.2 ± 4.5 minutes at 2.4 ± 0.5 km/h) to the last training session (40.5 ± 6.5 minutes at 2.9 ± 0.6 km/h; $t(14)=3.44$, $p=0.004$, $r=0.677$ and $t(14)=6.13$, $p<0.001$, $r=0.854$, respectively). The results of two participants could not be used for further statistical analysis due to time restrictions of one participant, technical malfunctioning and systematic non-response to Stroop stimuli during the obstacle avoidance task. Obstacle avoidance and Stroop success rates at pretest and posttest for all conditions were hence available for 13 participants.

Obstacle avoidance success rates

The obstacle avoidance success rate was $52.4\% \pm 16.3\%$ at the pretest and increased significantly by 24.5% (95% CI: 18.2 – 30.9%) to $77.0\% \pm 16.4\%$ at the posttest (Figure 3), as evidenced by a significant main effect of Time ($F(1,12)=70.27$, $p<0.001$, $\eta^2_p=0.854$). No main or interaction effects of Task were observed, indicating that the presence of Stroop stimuli had no effect on the obstacle avoidance success rate at pretest or at posttest (all $F(1,12) \leq 0.86$, $p \geq 0.372$, $\eta^2_p \leq 0.067$).

Stroop success rates

Stroop success rates increased significantly by 6.8% (95% CI: 1.1-12.5%) from pretest ($78.5\% \pm 14.2\%$) to posttest ($85.3\% \pm 14.8\%$, main effect of Time; $F(1,12)=6.85$, $p=0.023$, $\eta^2_p=0.363$). In addition, Stroop performance depended on the timing of stimulus presentation, as evidenced by a significant main effect of Instant ($F(2,24)=19.13$, $p<0.001$, $\eta^2_p=0.614$). Post-hoc analyses showed lowest success rates for Stroop stimuli presented during the obstacle-crossing maneuver, followed by Stroop stimuli presented directly after obstacle crossing and prior to obstacle crossing (Figure 4). Post-hoc analyses for the significant Time \times Instant interaction ($F(2,24)=4.67$, $p=0.019$, $\eta^2_p=0.280$) indicated that significant improvements in Stroop success rates from pretest to posttest were observed only for the obstacle-crossing stride (14.6% (95% CI: 5.0 – 24.3%); $t(12)=3.31$, $p=0.006$, $r=0.691$).

Stroop success rates during sitting and unobstructed walking (i.e., the control conditions) did not differ between pretest and posttest (Figure 4, $z=-1.05$, $p=0.293$, $r=-0.206$ and $z=-0.51$, $p=0.610$, $r=-0.100$, respectively). Only a

main effect of Condition was observed ($z=-2.49$, $p=0.013$, $r=0.489$), with higher Stroop success rates during sitting than during unobstructed walking (Figure 4). There was no significant interaction between Time and Condition ($z=-0.18$, $p=0.859$, $r=-0.035$).

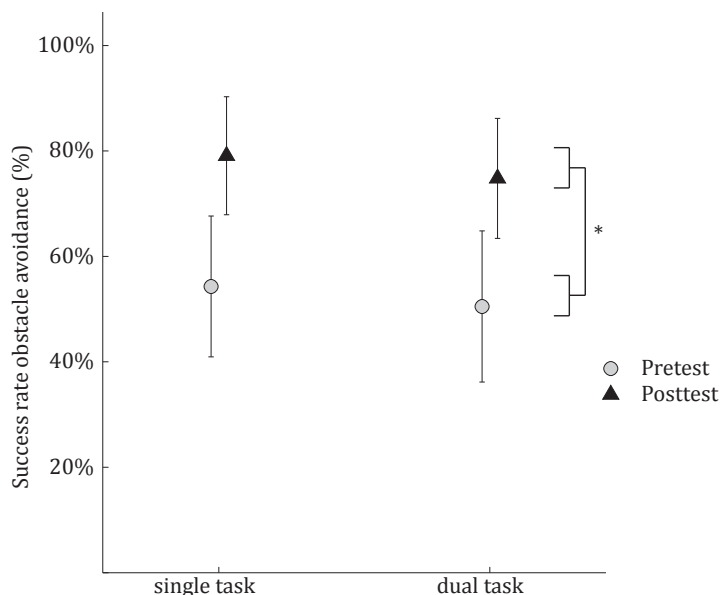


Figure 3. Obstacle avoidance success rates (mean [95% CI]) in single task (white) and dual task (grey) conditions at pretest and posttest. * Significant difference between pretest and posttest, $p \leq 0.001$

Discussion

The present pilot study sought to examine the concept of C-Mill gait adaptability training for improving step adjustments during walking and for reducing the associated attentional demands. We found that after 5-6 weeks of C-Mill training, participants showed significant improvements in obstacle avoidance performance. Moreover, obstacle crossing was not only more successful, but the associated step adjustments also required less attention, as demonstrated by improved Stroop performance during obstacle crossing. Interestingly, the use of the obstacle avoidance task, be it with or without performing a secondary auditory Stroop task, enabled us to compare our results with values of obstacle avoidance and Stroop success rates in the literature.^{8,10,11,18,33,36}

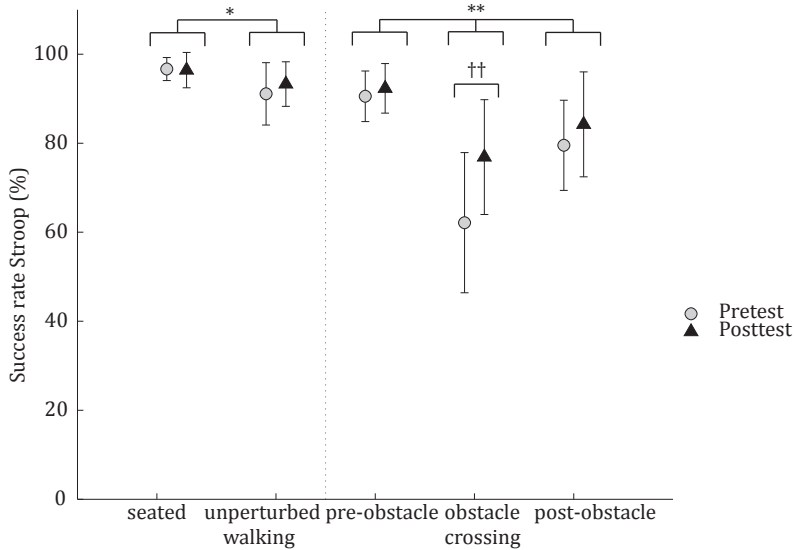


Figure 4. Stroop success rates (mean [95% CI]) at pretest (black circles) and posttest (grey squares) for stimuli presented pre-obstacle, during obstacle crossing, post-obstacle, and during sitting and unobstructed walking. Asterisks denote significant differences between instants of Stroop stimuli presentation, * $p \leq 0.05$, ** $p \leq 0.01$; †† Time \times Instant interaction effect, significant post-hoc effects between pretest and posttest, $p \leq 0.01$.

Gait adaptability

The participants in this study were high-functioning community ambulators, as evidenced by their excellent FAC and 10MWT scores (Table I). The obstacle avoidance success rate of 52.4% we observed before C-Mill training is comparable to that found by other recent studies in similar samples of persons after stroke,^{10,33} but is well below the 89-99.5% reported for healthy young and older adults.^{8,10,11,36} After C-Mill training, obstacle avoidance success rates increased for all participants and improved significantly to 77.0% on group level (Figure 3).

This improvement of 25% is more than twice as large compared to previously reported improvements with other task-specific gait-training interventions, such as an 8% improvement with functional electrical stimulation of the lower-limb muscles compared to an ankle-foot orthosis in persons with a drop foot due to stroke³³ and a 12% improvement in fall-prone elderly after five weeks of overground fall-prevention training.¹⁸ Moreover, the latter was accompanied by a significant reduction in fall incidence during one year follow-up. Recently, improvements in overground gait and obstacle avoidance tasks have also been observed after C-Mill training,²⁴ suggesting that improvements may carry over

to overground walking tasks. However, future randomized controlled trials are needed to confirm the potential of C-Mill training for improving safe community ambulation.

Attentional demands

In line with Smulders et al.,¹⁰ we observed that the presence of Stroop stimuli did not affect obstacle avoidance success rates. Nevertheless, Stroop success rates during the obstacle-crossing stride were significantly lower than those for the strides prior to and after obstacle crossing and also lower than the success rates observed for sitting and unobstructed walking (Figure 4). These results suggest that participants prioritized obstacle avoidance over the concurrent Stroop task performance, which is consistent with the so-called ‘posture first hypothesis’,³⁷ and confirm the finding by Smulders et al. that obstacle crossing is a highly attention-demanding task in people after stroke.¹⁰ This may cause problems during complex, daily-life situations that require gait adjustments while concurrently paying attention to secondary tasks. Interventions that successfully target attentional demands of adaptive walking are thus in place. Interestingly in that regard is our observation that Stroop success rates during obstacle crossing increased significantly after C-Mill training (Figure 4). Although the observed improvements in Stroop success rates could have been mediated by a speed-accuracy trade-off,³⁸ this is unlikely since secondary analyses^[see note A] in a subgroup of nine participants revealed that Stroop response times did not change from pretest to posttest. Thus, it seems fair to conclude that participants required less attention for obstacle avoidance after C-Mill training. Moreover, training-induced effects in attentional demands are likely task-specific as improvements were only noted during the obstacle-crossing maneuver and not for the other instants of Stroop stimuli presentation.

Thus far, the effect of gait adaptability training on the attentional demands of adaptive walking has not been studied in people after stroke. In other study populations, however, improvements in dual task performance after adaptive walking²⁰ or stepping^{39,40} training have been demonstrated. For example, Mirelman et al.²⁰ reported improved obstacle avoidance capacity as well as improved dual task gait speed after a period of virtual-reality treadmill training in persons with Parkinson’s disease, and recent pilot studies in older adults reported improvements in gait speed and voluntary step execution under dual task conditions after a 12-week cognitive-motor exercise program.^{39,40} The current study adds to these findings by showing that dual task performance during obstacle avoidance may improve after 5-6 weeks of C-Mill training in persons in the chronic stage after stroke.

Study limitations

The absence of a control group precluded evaluation of the added value of C-Mill training relative to other modalities of gait training. It also precluded control for learning effects on outcome measures. However, possible learning effects were minimized by including a familiarization session in the week prior to the pretest. Furthermore, pretests and posttests always started with six practice obstacle avoidance trials and with a practice Stroop task for one minute in a seated position. Therefore, possible learning effects with regard to obstacle avoidance or Stroop task performance are likely to be small. Besides, compared to the 25% improvement in obstacle avoidance success rates observed in the present study, much smaller improvements (6%) were observed in the inactive control group by Weerdesteyn et al.¹⁸ With respect to Stroop success rates, the absence of differences between pretest and posttest for all but the instant of obstacle crossing indicates that Stroop performance was not susceptible to learning effects. Yet, the significant differences in Stroop success rate among obstacle-crossing phases as well as between sitting and walking (Figure 4) demonstrate that this was not due to a ceiling effect and testify to the responsiveness of the Stroop task. Hence, we are confident that attentional demands of different tasks, as well as changes therein after interventions, can be validly assessed with the presently used paradigm.

This study included a small group of high-functioning community ambulators in the chronic stage after stroke, which reduces the generalization of the observed results. Although all participants showed improved obstacle avoidance success rates after 5-6 weeks of C-Mill training, it would be interesting to examine feasibility and benefits of C-Mill training in a wider range of stroke survivors. The generalization of results to improvements in safe community ambulation was also limited in the present study. Although Heeren et al.²⁴ recently demonstrated improvements in an overground obstacle avoidance task after C-Mill training, future studies should include overground gait adaptability testing and fall rate as important outcome measures to confirm the potential of C-Mill training for improving safe community ambulation.

In conclusion, the results of this pilot study suggest that C-Mill training may improve the ability to make step adjustments during walking and that these step adjustments require less attention. The study thus provides support and guidance for conducting a controlled trial with multiple follow-up measurements. Such a trial in a larger and wider patient sample and involving an active control group is warranted to confirm the potential of C-Mill training for improving safe community ambulation and to examine its contribution to the reduction of fall rate after stroke.

Note A

Stroop response times were calculated by subtracting stimulus onsets from response onsets. Stimulus and response onsets were defined as the moment that the audio signal exceeded the silence threshold (i.e., the mean value plus four standard deviations of the stimulus and response signals in silence). Individual median response times were used for statistical analysis. The Time by Stroop condition (2×5) repeated measures ANOVA revealed that Stroop response times did not differ significantly between pretest and posttest (pretest: 1.1 ± 0.1 s, posttest: 1.1 ± 0.1 s, $F(1,8)=1.09$, $p=0.327$, $\eta^2=0.120$). In addition, no significant Time \times Stroop condition interaction was revealed ($F(4,32)=1.19$, $p=0.332$, $\eta^2=0.130$). Analyses only revealed a significant main effect of Stroop condition ($F(4, 32)=23.73$, $p<0.001$, $\eta^2=0.748$), with the highest response times observed for Stroop stimuli presented during the obstacle-crossing maneuver.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. Jan 1 2013;127(1):143-52.
2. Friedman PJ. Gait recovery after hemiplegic stroke. *Int Disabil Stud*. Jul-Sep 1990;12(3):119-22.
3. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil*. Jan 1995;76(1):27-32.
4. Weerdesteyn V, de Niet M, van Duijnhoven HJ, Geurts AC. Falls in individuals with stroke. *J Rehabil Res Dev*. 2008;45(8):1195-213.
5. Hyndman D, Ashburn A, Stack E. Fall events among people with stroke living in the community: circumstances of falls and characteristics of fallers. *Arch Phys Med Rehabil*. Feb 2002;83(2):165-70.
6. Roerdink M, Lamothe CJ, van Kordelaar J, et al. Rhythm perturbations in acoustically paced treadmill walking after stroke. *Neurorehabil Neural Repair*. Sep 2009;23(7):668-78.
7. Houdijk H, van Ooijen MW, Kraal JJ, et al. Assessing gait adaptability in people with a unilateral amputation on an instrumented treadmill with a projected visual context. *Phys Ther*. Nov 2012;92(11):1452-60.
8. Den Otter AR, Geurts AC, de Haart M, Mulder T, Duysens J. Step characteristics during obstacle avoidance in hemiplegic stroke. *Exp Brain Res*. Feb 2005;161(2):180-92.
9. Said CM, Goldie PA, Patla AE, Sparrow WA, Martin KE. Obstacle crossing in subjects with stroke. *Arch Phys Med Rehabil*. Sep 1999;80(9):1054-9.
10. Smulders K, van Swigchem R, de Swart BJ, Geurts AC, Weerdesteyn V. Community-dwelling people with chronic stroke need disproportionate attention while walking and negotiating obstacles. *Gait Posture*. May 2012;36(1):127-32.
11. van Swigchem R, van Duijnhoven HJ, den Boer J, Geurts AC, Weerdesteyn V. Deficits in motor response to avoid sudden obstacles during gait in functional walkers poststroke. *Neurorehabil Neural Repair*. Mar 2013;27(3):230-9.
12. Hyndman D, Ashburn A. Stops walking when talking as a predictor of falls in people with stroke living in the community. *J Neurol Neurosurg Psychiatry*. Jul 2004;75(7):994-7.
13. Hyndman D, Ashburn A, Yardley L, Stack E. Interference between balance, gait and cognitive task performance among people with stroke living in the community. *Disabil Rehabil*. Jul 15-30 2006;28(13-14):849-56.
14. Canning CG, Ada L, Paul SS. Is automaticity of walking regained after stroke? *Disabil Rehabil*. Jan 30 2006;28(2):97-102.
15. Roerdink M, Beek PJ, Inventors; ForceLink BV, assignee. Device for displaying target indications for foot movements to persons with a walking disorder. US patent 2009246746-A1 (October 1, 2009), European patent 2106779-A1 (October 7, 2009), Japanese patent 2009240775-A (October 22, 2009), and Dutch patent 1035236-C2 (October 1, 2009). 2009.

16. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* Aug 2009;8(8):741-54.
17. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet.* May 14 2011;377(9778):1693-702.
18. Weerdesteyn V, Rijken H, Geurts ACH, Smits-Engelsman BCM, Mulder T, Duysens J. A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly. *Gerontology.* 2006;52(3):131-41.
19. Yamada M, Aoyama T, Arai H, et al. Complex obstacle negotiation exercise can prevent falls in community-dwelling elderly Japanese aged 75 years and older. *Geriatr Gerontol Int.* Jul 2012;12(3):461-7.
20. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual Reality for Gait Training: Can It Induce Motor Learning to Enhance Complex Walking and Reduce Fall Risk in Patients With Parkinson's Disease? *J Gerontol A Biol Sci Med Sci.* Feb 2011;66(2):234-40.
21. Jaffe DL, Brown DA, Pierson-Carey CD, Buckley EL, Lew HL. Stepping over obstacles to improve walking in individuals with poststroke hemiplegia. *J Rehabil Res Dev.* May 2004;41(3A):283-92.
22. Yang YR, Tsai MP, Chuang TY, Sung WH, Wang RY. Virtual reality-based training improves community ambulation in individuals with stroke: a randomized controlled trial. *Gait Posture.* Aug 2008;28(2):201-6.
23. Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. *Neurorehabil Neural Repair.* Mar-Apr 2009;23(3):197-206.
24. Heeren JHM, van Ooijen MW, Geurts AC, et al. Step by step; A proof of concept study of C-Mill gait adaptability training in the chronic phase after stroke. *Journal of Rehabilitation Medicine.* 2013;in press.
25. Weerdesteyn V, Schillings AM, van Galen GP, Duysens J. Distraction affects the performance of obstacle avoidance during walking. *J Mot Behav.* Mar 2003;35(1):53-63.
26. Schillings AM, Van Wezel BM, Duysens J. Mechanically induced stumbling during human treadmill walking. *J Neurosci Methods.* Jul 1996;67(1):11-7.
27. Cohen G, Martin M. Hemisphere differences in an auditory Stroop test. *Percept Psychophys.* 1975;17(1):79-83.
28. Mehrholz J, Wagner K, Rutte K, Meissner D, Pohl M. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. *Arch Phys Med Rehabil.* Oct 2007;88(10):1314-9.
29. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. *J Neurol Neurosurg Psychiatry.* Jul 1990;53(7):576-9.
30. Gladstone DJ, Danells CJ, Black SE. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehabil Neural Repair.* Sep 2002;16(3):232-40.
31. Pestronk A, Florence J, Levine T, et al. Sensory exam with a quantitative tuning fork: rapid, sensitive and predictive of SNAP amplitude. *Neurology.* Feb 10 2004;62(3):461-4.
32. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of

- impairment and disability. *Int Disabil Stud.* Jan-Mar 1990;12(1):6-9.
33. van Swigchem R, van Duijnhoven HJ, den Boer J, Geurts AC, Weerdesteyn V. Effect of peroneal electrical stimulation versus an ankle-foot orthosis on obstacle avoidance ability in people with stroke-related foot drop. *Phys Ther.* Mar 2012;92(3):398-406.
 34. Weerdesteyn V, Nienhuis B, Hampsink B, Duysens J. Gait adjustments in response to an obstacle are faster than voluntary reactions. *Hum Mov Sci.* Oct 2004;23(3-4):351-63.
 35. Field A. *Discovering statistics using SPSS.* third edition ed: Sage Publications; 2009.
 36. Weerdesteyn V, Nienhuis B, Geurts AC, Duysens J. Age-related deficits in early response characteristics of obstacle avoidance under time pressure. *J Gerontol A Biol Sci Med Sci.* Sep 2007;62(9):1042-7.
 37. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture.* Aug 2002;16(1):1-14.
 38. Wickelgren WA. Speed-accuracy tradeoff and information processing dynamics. *Acta Psychologica.* 1977;41(1):67-85.
 39. De Bruin ED, Reith A, Dorflinger M, Murer K. Feasibility of Strength-Balance Training Extended with Computer Game Dancing in Older People; Does it affect Dual Task Costs of Walking? *J Novel Phys.* 2011;1(1):1-7.
 40. Pichierri G, Coppe A, Lorenzetti S, Murer K, de Bruin ED. The effect of a cognitive-motor intervention on voluntary step execution under single and dual task conditions in older adults: a randomized controlled pilot study. *Clin Interv Aging.* 2012;7:175-84.

Part II

Cognitive control of
gait and balance in
patients with Parkinson's disease

Chapter 4

Assessment of dual tasking has no clinical value for fall prediction in Parkinson's disease

Katrijn Smulders, Rianne Esselink, Aner Weiss, Roy Kessels,
Alexander Geurts, Bastiaan Bloem

Journal of Neurology 2012; 259(9):1840-7



Abstract

Background: The objective of this study was to investigate the value of dual task performance for the prediction of falls in patients with Parkinson's disease (PD).

Methods: 263 patients with PD (H&Y 1-3, 65.2 ± 7.9 yrs) walked two times along a 10 m trajectory, both under single task (ST) and dual task (DT) conditions (combined with an auditory Stroop task). To control for a cueing effect, Stroop stimuli were presented at variable or fixed 1- or 2-second intervals. The auditory Stroop task was also performed alone. Dual task costs were calculated for gait speed, stride length, stride time, stride-time variability, step and stride regularity, step symmetry and for Stroop composite scores (accuracy/reaction time). Subsequently, falls were registered prospectively during one year (monthly assessments). Patients were categorized as non-recurrent fallers (no or 1 fall) or recurrent fallers (>1 falls).

Results: Recurrent fallers (35%) had a significantly higher disease severity, lower MMSE scores, and higher TUG test scores than non-recurrent fallers. Under DT conditions, gait speed and stride lengths were significantly decreased. Stride time, stride-time variability, step and stride regularity and step symmetry did not change under DT conditions. Stroop dual task costs were only significant for the 2s Stroop interval trials. Importantly, recurrent fallers did not show different dual task costs compared to non-recurrent fallers on any of the gait or Stroop parameters. These results did not change after correction for baseline group differences.

Conclusion: Deterioration of gait or Stroop performance under dual task conditions was not associated with prospective falls in this large sample of patients with PD.

Introduction

Falling is a common and incapacitating complication of Parkinson's disease (PD).¹ Even in early disease stages a considerable number of patients with PD fall.² To identify these fallers, it is necessary to develop a sensitive and specific measure to timely predict which patients are at high risk of future falls. This is still not adequately possible using existing prediction algorithms.

Lundin-Olsson was the first to demonstrate that older people who stop walking while talking had a higher risk of falling than those who are able to continue walking.³ Since then, the dual task paradigm has been regarded as a promising way of discriminating between people at risk of falls and those who are not.⁴ Gait deficits generally call for increased attentional demands in order to maintain stability and prevent stumbling. A well-proven paradigm to assess attentional demands of gait is to add a secondary cognitive task, and to compute the cost of dual tasking.^{5,6} That is, performing a cognitive task while walking leads to a situation in which two tasks compete for the same attentional resources.⁷ When the attentional demands of both tasks together exceed the available capacity, the performance of one or both tasks will deteriorate compared to the respective single task performance.

In patients with PD, dual task situations are thought to be extra challenging since executive function is often impaired even in early stages of the disease.⁸ Specifically, PD affects the ability to flexibly switch from one attentional set to another.^{9,10} Impaired set-shifting further complicates dual task situations in which attention needs to be properly allocated to the tasks at hand. When people are walking and are concurrently engaged in a cognitive task, the most sensible strategy to maintain stability is to prioritize posture, thereby decreasing the risk of falling. This notion is called the 'posture first hypothesis'.⁶ However, Bloem and colleagues found that patients with PD actually gave less priority to motor tasks than healthy participants, possibly placing them at a higher risk of falls.¹¹

In healthy people, gait adaptations under dual task conditions include slowing of gait speed and reducing stride length.¹² The same adaptations have been observed in patients with PD,¹³⁻¹⁵ but their gait variability is also increased under dual task conditions.^{16,17} Furthermore, gait variability in a single task condition has been associated with fall risks in PD.¹⁸ Taken together, this has led to the suggestion that increased gait variability under dual task conditions may be a predictor of falling in patients with PD.^{5,19}

The aim of the present study was to investigate whether dual task performance predicts falling in patients with PD. For this purpose, we evaluated a gait task and a cognitive task (auditory Stroop task) during single task and dual task conditions in a large cohort of patients that was prospectively monitored for fall

incidence. Fall incidence was accurately monitored for a period of one year after the functional assessments.

Methods

Participants

The present sample was a subset of the 586 idiopathic patients with PD participating in the ParkFit study, a multicentre randomized clinical trial aiming to evaluate the effectiveness of a behavioral program promoting physical activity.²⁰ Eligibility criteria of the ParkFit study were idiopathic PD with Hoehn and Yahr ≤ 3 , aged between 40-75 years with a sedentary lifestyle. Exclusion criteria were: unclear diagnosis, MMSE < 24 , unable to complete Dutch questionnaires, severe co-morbidity, daily institutionalized care and deep brain surgery. The present study was approved by the regional medical ethical committee (CMO region Arnhem-Nijmegen) and patients gave their written informed consent before the first assessment.

A total of 332 patients participated in the present dual task study. Due to errors during recording or storing of the Stroop task ($n=17$) and gait task ($n=11$), weakness of recorded Stroop response signals ($n=6$), inability to understand the Stroop task while seated ($n=21$), or incomplete fall records ($n=14$), analysis was performed on 263 patients (64.6% male; 65.2 ± 7.9 years; Table 1).

Clinical assessment (Table 1)

To assess the severity of motor symptoms we used the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III).²¹ Hoehn and Yahr staging (H&Y) was used to assess disease stage.²² A global index of cognitive function was obtained using the Mini-Mental State Examination (MMSE).²³ Level of education was assessed using six categories, ranging from 'no education' (1) to 'university degree' (6). The Timed "Up & Go" (TUG) test was used as an index of mobility.²⁴ In the TUG test the patient has to stand up from a chair, walk 3 m at comfortable speed, turn 180°, walk back to the chair and sit down again as fast as possible while time is recorded.

Gait task

Subjects were assessed while walking along a regular walkway of 10 m length. Under both single task and the various dual task conditions, each subject completed two trials. Subjects were instructed to walk at their normal pace. Gait parameters were measured with a triaxial accelerometer sampling with 100 Hz

(Dynaport, McRoberts) attached to the lower back at the pelvis. The Dynaport accelerometer detects steps with 5.6% error and step duration with 9.9% error in patients with PD.²⁵

Analysis of gait parameters was performed in Matlab (MathWorks). Temporal gait parameters were calculated using heel strike detection algorithms. Gait speed, stride length, stride time and stride time variability were calculated. Step and stride regularity and step symmetry were derived from frequency analysis of vertical acceleration signals using unbiased autocorrelation.²⁶ Perfect regularity (i.e. no variability) and symmetry result in correlation coefficients of 1. For all gait parameters, scores over the first and second 10m walk were averaged.

Table 1. Demographic and clinical characteristics of the participants.

	Total (N=263)	Non-recurrent fallers (N=171)	Recurrent fallers (N=91)	p value
Age (yrs)	65.2 ± 7.9	64.6 ± 8.1	66.3 ± 7.5	0.099
Gender (% men)	64.6%	65.7%	62.6%	0.621
UPDRS-III	34.1 ± 9.4	32.7 ± 9.1	36.7 ± 9.4	0.001
H&Y stage (mode) 1	9 (3%)	6 (4%)	3 (4%)	0.724
2	248 (94%)	163 (95%)	85 (93%)	
3	6 (2%)	3 (2%)	3 (3%)	
MMSE	28.2 ± 1.6	28.3 ± 1.5	27.8 ± 1.7	0.012
Educational level (mode)	3	3	3	0.873
Timed "Up and Go" (s)	9.5 ± 2.9	9.1 ± 2.9	10.3 ± 2.7	0.003
Falls (n)	689	48	641	<0.001

UPDRS-III = Unified Parkinson's Disease Rating Scale motor examination; H&Y = Hoehn & Yahr; MMSE = Mini-Mental State Examination

Cognitive task

We selected an auditory Stroop task as the secondary cognitive task.²⁷ During this task participants hear the word "high" or "low" in a high or low pitch and are instructed to name the pitch of the stimulus, thus ignoring the meaning of the word. Two conditions are defined: congruent stimuli in which the word and pitch are equal (e.g. "high" at a high pitch), and incongruent stimuli in which the two differ (e.g. "high" at a low pitch). Participants were instructed to respond as accurately and as fast as possible. Before actual measurements, a series of ten Stroop stimuli was practiced.

The stimuli were played by a digital recorder (Micro BR, Boss Corporation) and

presented through a headphone with an integrated microphone in a mouthpiece (Sennheiser PC130, Sennheiser). The verbal responses of the subjects were recorded and saved on a digital card (sample frequency 44.1 kHz).

Stroop stimuli of three different complexity levels were presented by varying the interval between stimuli: 1-second intervals, 2-second intervals and variable (1-, 2- or 3-second) intervals. The latter condition was introduced to evaluate a possible cueing effect of the Stroop task on gait.²⁸

The accuracy of all Stroop responses was scored manually. Onsets of verbal responses were detected and visually inspected in Matlab. Verbal reaction time was calculated as the difference between the start of the stimulus and the start of the response. To account for possible speed-accuracy trade-off, a composite score was calculated by dividing accuracy (% correct responses) by verbal reaction time (ms).²⁹ Only reaction times of correct answers were used in the composite score.

Procedure

All subjects performed both the Stroop task and the gait task as a single task and during dual task conditions. The three single task conditions of the Stroop task (1s, 2s and variable interval) were tested while patients were seated. During the dual task conditions, participants walked while simultaneously responding to each of the three Stroop conditions. No instruction with regard to task priority was given.

Half of the participants started with the single task Stroop and single task walk followed by the dual task condition, whereas others started with the dual task conditions followed by the single task conditions. The order of the Stroop conditions was counterbalanced between subgroups of patients, but was equal for the single and dual task conditions.

Falls assessment

In the year following the functional assessments, falls were registered monthly using an automated system to monitor falls over the telephone (Falls Telephone, ASK Community Systems). The Falls Telephone called participants every month and asked them how many times they had fallen in the previous month. The Falls Telephone has been tested and found to be a reliable instrument to monitor falls in PD with a sensitivity of 100% and specificity of 78%.³⁰ To further increase specificity, all fall entries were verified by a personal telephone call of trained research assistants.

Participants were divided into two groups based on the number of falls: patients with no or a single fall over 12 months (non-recurrent fallers) and

patients who had fallen more than once during 12 months (recurrent fallers).³¹

Data analysis

Differences between recurrent and non-recurrent fallers on demographic and clinical characteristics, single task walking and single task Stroop performance were evaluated using Student's t-tests for independent samples in the case of continuous variables and chi-square tests in the case of categorical variables. In order to remove skewness, single task and dual task scores were logtransformed before analysis. Dual task effects were assessed by a one-sample t-test.

Dual task costs for the gait parameters and for the Stroop composite scores were calculated as the ratio between DT and ST performance. Dual task costs were calculated separately for the three dual task conditions. Differences in dual task costs between recurrent and non-recurrent fallers were analyzed with 3x2 (Stroop condition x group) ANOVA with repeated measures (ANOVA-RM). In the case of significant main effects, Bonferroni-corrected post-hoc analyses were carried out. To correct for baseline differences between groups, ANCOVA-RM analyses were performed with all clinical and demographic variables that were significantly different between groups as co-variables. For all analyses, significance was accepted at $p < 0.05$ (two-sided).

Finally, in order to gain insight into the strategy used under dual task conditions for both groups, dual task costs for the Stroop task (2s interval) were plotted against dual task costs for walking (gait speed) for each patient. In this plot patients using a posture first strategy (high cognitive dual task costs, low motor dual task costs) are positioned differently compared to patients with a posture second strategy (equally high dual task costs for both tasks, or high costs for walking).

Results

Baseline characteristics of recurrent fallers vs non-recurrent fallers

One-hundred seventy-one patients with PD (65%) appeared to be non-recurrent fallers. The remaining 91 patients (35%) experienced a total of 661 falls. Recurrent fallers had significantly higher UPDRS-III scores ($p < 0.001$), lower MMSE scores ($p = 0.012$), and lower TUG scores ($p = 0.003$). Age ($p = 0.099$), gender ($p = 0.621$), H&Y stage ($p = 0.724$) and educational level ($p = 0.873$) were not significantly different between the groups. Detailed characteristics of the two groups are presented in Table 1.

Gait and Stroop outcome measures of the single task conditions are presented in Table 2. Recurrent fallers had significantly lower gait speed ($p = 0.041$) and

smaller stride length ($p=0.012$) compared to non-recurrent fallers. Stride time, stride time variability, step and stride regularity, and step symmetry did not differ significantly between groups (all $p>0.05$). In addition, no (significant) differences between groups were observed for Stroop composite scores on congruent or incongruent stimuli (all $p\geq 0.472$).

Table 2. Single task gait and Stroop outcomes^a

	Non- recurrent fallers	Recurrent fallers	% difference (CI)	p value
Gait				
Speed (m.s ⁻¹)	1.00 (0.17)	0.95 (0.17)	5.3 (0.2 – 10.6)	0.041
Stride length (m)	1.26 (0.21)	1.19 (0.20)	5.8 (1.2 – 10.6)	0.012
Stride time (s)	1.13 (0.11)	1.16 (0.20)	-1.9 (-4.6 – -0.8)	0.168
Stride time variability (%)	10.38 (8.18)	10.80 (8.14)	-7.7 (-23.4 – 11.3)	0.401
Step regularity	0.68 (0.14)	0.64 (0.14)	5.8 (-1.3 – 13.4)	0.113
Stride regularity	0.70 (0.10)	0.67 (0.13)	5.0 (-0.2 – 10.4)	0.058
Step symmetry	0.97 (0.14)	0.96 (0.16)	0.8 (-3.6 – 5.3)	0.733
Stroop task				
Congruent stimuli				
1s	1.02 (0.27)	0.95 (0.32)	3.6 (-6.1 – 14.4)	0.478
2s	1.46 (0.52)	1.45 (0.47)	-2.2 (-11.5 – 8.0)	0.874
Variable	1.01 (0.25)	1.01 (0.25)	-0.8 (-10.7 – 10.1)	0.472
Incongruent stimuli				
1s	0.93 (0.27)	0.80 (0.27)	2.4 (-7.9 – 13.8)	0.656
2s	1.25 (0.45)	1.10 (0.41)	3.0 (-5.0 – 11.6)	0.664
Variable	0.80 (0.28)	0.74 (0.26)	-0.5 (-12.2 – 13.9)	0.937

P-values in bold are significant differences between recurrent and non-recurrent fallers ($p<0.05$). Abbreviations: 1s = 1 second interval between stimuli; 2s = 2 second interval between stimuli; Variable = variable interval between stimuli.

^a Data are presented as means (sd).

Effect of Stroop task on gait performance

Dual task costs are presented in Figure 1. Adding the Stroop task to walking resulted in a significantly lower gait speed for all Stroop conditions (all $p < 0.001$). Stride length was significantly shortened during all Stroop conditions as well (all $p < 0.001$), but stride time was significantly shortened only in the 2s Stroop condition ($p = 0.006$). Step regularity was negatively affected only in the variable Stroop interval condition ($p = 0.027$). Stride time variability, stride regularity, and step symmetry were not changed under dual task conditions in any of the Stroop conditions (all $p \geq 0.364$).

The ANOVA-RM analysis yielded a main effect of Stroop condition on gait speed ($F_{2,259} = 15.76, p < 0.001$) and stride time ($F_{2,260} = 7.216, p = 0.001$), but not on all other gait parameters (all $p > 0.008$). Post-hoc analyses revealed that dual task costs for gait speed and stride time were higher in the 2s-interval compared to 1s-interval condition (all $p \leq 0.001$), and that dual task costs for gait speed were higher in the variable-interval than in 1s-interval condition ($p < 0.001$).

Effect of gait on Stroop task performance

Dual task effects on Stroop task performance were only significant for the 1s-interval condition responding to incongruent stimuli ($t_{1,248} = -3.700, p < 0.001$, Figure 1).

Dual task cost in recurrent fallers vs. non-recurrent fallers

Dual task effects on the different gait and Stroop parameters were compared between non-recurrent fallers and recurrent fallers using ANOVA-RM. This analysis yielded no significant group effects on gait speed ($F_{2,259} = 0.20, p = 0.657$), stride length ($F_{2,260} = 0.02, p = 0.878$), stride time ($F_{2,260} = 0.05, p = 0.821$), stride-time variability ($F_{2,260} = 0.23, p = 0.629$), step regularity ($F_{2,260} = 0.09, p = 0.768$), stride regularity ($F_{2,260} = 0.02, p = 0.876$), or step symmetry ($F_{2,260} = 0.014, p = 0.905$). Likewise, dual task costs for the Stroop task did not differ significantly between groups ($F_{2,260} = 0.175, p = 0.676$).

Because the recurrent fallers had higher UPDRS-III scores, slower TUG test performance, and lower MMSE scores, the analyses were repeated with these variables as co-variates in the model. However, this did not alter our results in that no significant differences between recurrent fallers and non-recurrent fallers were found for any of the gait and Stroop outcomes.

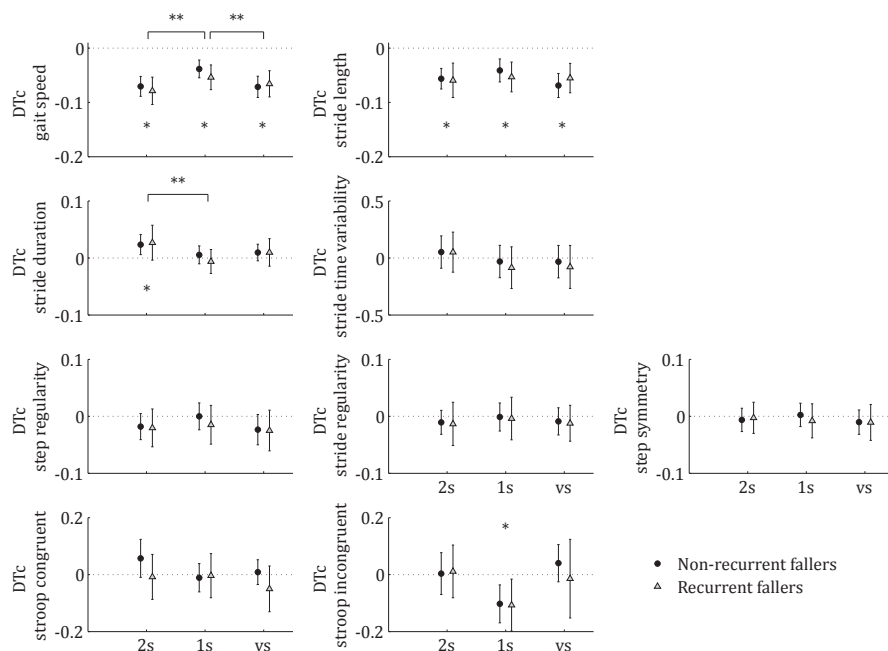


Figure 1. Dual task costs are plotted for the different gait parameters and the Stroop performance. Dual task costs were calculated as the ratio between DT and ST performance. Dotted lines depict no dual task costs (e.g. no difference between single and dual task). Positive dual task costs indicate higher scores in dual task condition compared to single task condition. Data are log-transformed means and CI. The three Stroop conditions are presented on the x-axis; Stroop intervals of 2 seconds (2s), 1 second (1s) and a variable interval (1-3 seconds) were used. Abbreviations: DTc = dual task cost

* Significant dual task costs ** Significant differences between Stroop intervals

Descriptive analysis of priority

In order to analyze whether recurrent fallers used a different priority strategy under dual task conditions compared to non-recurrent fallers, the individual dual task costs for the Stroop task (2s) were plotted against the dual task costs for walking speed. As can be seen in Figure 2, the positions of the recurrent fallers in the plot did not substantially differ from those of the non-recurrent fallers. Even in the group of frequent fallers (> 5 falls/year; larger dots in Figure 2) we could not determine different priority strategies (e.g. posture second) compared to non-fallers.

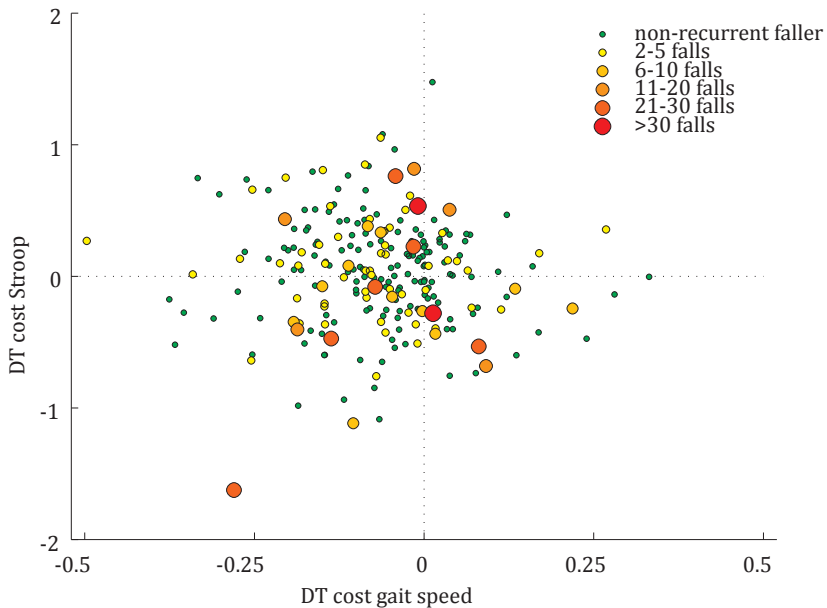


Figure 2. Dual task (DT) costs for the Stroop task plotted against dual task costs for gait speed for each individual. Negative DT costs indicate a deterioration of performance in DT condition compared to single task condition. A DT cost of 0 indicates that ST and DT performance was equal.

Discussion

In this large-scale study we evaluated if dual task performance was associated with future falls in patients with PD. The major finding was that patients with PD with recurrent falls did not have higher dual task costs than patients without recurrent falls. This was found for all gait and Stroop outcomes. Second, recurrent fallers walked slower than non-recurrent fallers under single task conditions and scored worse on clinical motor tests. Third, recurrent fallers did not use a different (e.g. posture second) strategy in prioritizing the various tasks compared to non-recurrent fallers.

The similarity in dual task costs between recurrent and non-recurrent fallers is largely in accordance with the only existing dual task study to date that examined a small sample of fallers and non-fallers with PD.¹⁹ This study reported similar dual task effects on gait speed, stride length, stride time variability, and gait symmetry in both groups. This study, however, did find small, yet significant differences between fallers and non-fallers on swing time variability. We were unable to differentiate between swing and stance phase of the gait cycle and

were therefore unable to replicate this finding.

In older people, significant associations between dual tasking during walking and falls have been reported in a pooled analysis of different dual task studies.⁴ Importantly, only two studies have analyzed the added value of dual task over single task walking in predicting falls.^{32,33} In both studies, dual task walking was as good in predicting fall risks as single task walking. Another important observation was that dual task walking only predicted falls in institutionalized elderly, as opposed to community-dwelling people. Thus, the predictive value of dual task parameters for fall risk may be restricted to more frail elderly than we studied in our present cohort of community ambulators.

Although recurrent fallers did not show different dual task effects, they performed significantly worse on clinical motor tests and gait parameters than non-recurrent fallers. The most prominent differences between recurrent fallers and non-recurrent fallers were more severe motor symptoms (UPDRS-III), slower TUG performance, lower gait speed and shorter stride length during single task walking. These findings confirm those of previous studies demonstrating the predictive value of clinical balance and mobility measures,^{2,34} and single task walking for falls in PD.^{18,19}

In addition to motor characteristics, cognitive dysfunction (and particularly executive dysfunction) predisposes patients with PD to falls,^{34,35} perhaps because of difficulties in allocating and shifting attention in multiple-task situations.¹² It could therefore be expected that impaired executive function leads to difficulties in dual task conditions and, consequently, may make participants more prone to falls. In our study sample of relative early stage patients with PD, recurrent fallers showed a lower performance on global cognition (MMSE), but differences in Stroop task performance were absent at baseline. Since the Stroop task relies on executive function, specifically response inhibition,³⁶ the specific role of executive dysfunction in fall risk could not be confirmed in our study.

To gain insight into priority setting when allocating attention in multiple tasks, the dual task costs for gait parameters were compared to those of the Stroop task. The “posture second” hypothesis as suggested by Bloem implies that in dual task conditions patients with PD do not adequately allocate attention to walking, placing them at risk of postural instability and falls.⁵ Although we could not test this hypothesis statistically, the visualization of dual task costs for both tasks in Figure 2 does not provide support for this hypothesis. Patients in our cohort applied a variety of strategies, but recurrent fallers and non-recurrent fallers did not consistently show different preferences in the dual task costs for gait compared to Stroop task performance. In order to further objectify priority strategy during multiple tasks, future research should focus on detecting

reference values above which dual task costs are detrimental for daily life gait and balance in healthy participants and people with gait and balance impairments.

Gait was slower under dual task conditions presumably because of smaller stride lengths. This change in gait pattern implies that the attentional capacity was exceeded during dual tasking. Dual task deficits in PD have been reported frequently in various combinations of tasks.³⁷ A neuroimaging study revealed that patients with PD showed increased brain activity while performing dual tasks compared to healthy participants,³⁸ probably reflecting an attempt to compensate for dysfunction of the basal ganglia. Whether such dual task abnormalities are caused by limited attentional resources, increased attentional demands for the separate tasks (due to less automatic movements), or from an impairment to switch between tasks remains to be clarified.

In contrast to our expectation, variability of gait was unaffected in the dual task conditions. A cueing effect of the Stroop task may underlie this finding since an external cue can improve stride time-variability in PD.²⁸ In order to detect a potential cueing effect induced by the Stroop task, we introduced a condition with variable intervals between stimuli. The mean interval of the variable-interval Stroop condition was comparable to the 2s Stroop condition, and no differences between the two tasks were observed in the dual task costs. However, this does not rule out the possibility of a cueing effect improving gait speed and variability in the faster 1s Stroop task.

Some limitations of our study merit attention. Our cohort consisted of a large, homogeneous sample of mild to moderate patients with PD, all being community ambulators. Generalization to more severe patients with PD should, therefore, be done with caution. With disease progression, gait and postural deficits as well as cognitive impairments may result in larger dual task costs that are potentially associated with falls. Also, all patients had to have a sedentary lifestyle in order to be eligible for the study. This selection may have influenced the incidence of falls, since an active lifestyle has been associated with reduced fall rates because of positive effects on strength and balance.³⁹ On the contrary, higher exposure to balance-threatening situations during exercise could increase the risk of falling. Importantly, even in this relatively 'early' and sedentary PD cohort, falls were common. Consequently, better identification of patients at risk to sustain a (first) fall remains needed in order to timely install fall prevention programs.

Another limitation of the present study is that walking circumstances were fairly optimal. Participants walked over even ground without obstacles. In daily life, obstacles and uneven terrain have to be overcome while walking, leading to higher attentional demands. It is possible that dual task deficits leading to instability and falls in daily life have remained undetected in this study, because of

the relatively simple walking task. Obstacle avoidance tasks or more challenging walking circuits are alternatives to be used in dual task studies to further clarify the potential role of dual task deficits in falling.^{11,40} Finally, we assessed gait variability as the average of two trajectories of 10 m, enabling us to measure this large sample of patients with PD. Ideally, a continuous walking distance of minimal 20 m is used to measure gait variability.⁴¹

In conclusion, the present findings from this large cohort study do not support the use of dual task paradigms for the prediction of falls in patients with mild to moderate Parkinson's disease. With the current knowledge, future falls in community-dwelling patients with mild to moderate PD can be better predicted using relatively simple clinical tests such as the UPDRS and freezing of gait questionnaire.²

References

1. Pickering RM, Grimbergen YA, Rigney U, et al. A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov Disord.* Oct 15 2007;22(13):1892-900.
2. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA. Predictors of future falls in Parkinson disease. *Neurology.* Jul 13 2010;75(2):116-24.
3. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. *The Lancet.* 1997;349(9052):617-.
4. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? *Eur J Neurol.* Jul 2009;16(7):786-95.
5. Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci.* 2006;248(1-2):196-204.
6. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture.* 2002;16(1):1-14.
7. Kahneman D. Attention and task interference. In: Kahneman D, ed. *Attention and Effort.* Englewood-Cliffs, New Jersey: Prentice-Hall; 1973:178-201.
8. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology.* 2005;65(8):1239-45.
9. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain.* 2001;124(Pt 12):2503-12.
10. Helmich RC, Aarts E, de Lange FP, Bloem BR, Toni I. Increased dependence of action selection on recent motor history in Parkinson's disease. *J Neurosci.* 2009;29(19):6105-13.
11. Bloem BR, Valkenburg VV, Slabbekoorn M, van Dijk JG. The multiple tasks test. Strategies in Parkinson's disease. *Exp Brain Res.* 2001;137(3-4):478-86.
12. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-42.
13. Canning CG, Ada L, Johnson JJ, McWhirter S. Walking capacity in mild to moderate Parkinson's disease. *Arch Phys Med Rehabil.* Mar 2006;87(3):371-5.
14. Rochester L, Hetherington V, Jones D, et al. Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Arch Phys Med Rehabil.* 2004;85(10):1578-85.
15. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci.* 2005;22(5):1248-56.
16. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol.* Mar 2003;16(1):53-8.
17. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. *J Neurol Neurosurg Psychiatry.* Mar 2009;80(3):347-50.
18. Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci.* Aug 15 2003;212(1-2):47-53.
19. Plotnik MP, M., Giladi N, Dagan Y, Hausdorff JM. Postural instability and fall risk in

- Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. *Exp Brain Res*. May 2011;210(3-4):529-38.
20. Van Nimwegen M, Speelman AD, Smulders K, et al. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. *BMC Neurol*. 2010;10:70.
 21. Fahn S, Elton RL, Committee UD. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Healthcare Information; 1987:153-63.
 22. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967;17(5):427-42.
 23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-98.
 24. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-8.
 25. Dijkstra B, Zijlstra W, Scherder E, Kamsma Y. Detection of walking periods and number of steps in older adults and patients with Parkinson's disease: accuracy of a pedometer and an accelerometry-based method. *Age Ageing*. Jul 2008;37(4):436-41.
 26. Moe-Nilssen R, Helbostad JL. Estimation of gait cycle characteristics by trunk accelerometry. *J Biomech*. Jan 2004;37(1):121-6.
 27. Cohen G, Martin M. Hemisphere differences in an auditory Stroop test. *Percept Psychophys*. 1975;17(1):79-83.
 28. Baker K, Rochester L, Nieuwboer A. The effect of cues on gait variability--reducing the attentional cost of walking in people with Parkinson's disease. *Parkinsonism Relat Disord*. 2008;14(4):314-20.
 29. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord*. 2006;21(7):950-7.
 30. Van der Marck MA, Overeem S, Klok PC, Bloem BR, Munneke M. Evaluation of the falls telephone: an automated system for enduring assessment of falls. *J Am Geriatr Soc*. Feb 2011;59(2):340-4.
 31. Mak MK, Pang MY. Parkinsonian single fallers versus recurrent fallers: different fall characteristics and clinical features. *J Neurol*. Sep 2010;257(9):1543-51.
 32. Beauchet O, Allali G, Annweiler C, et al. Does change in gait while counting backward predict the occurrence of a first fall in older adults? *Gerontology*. 2008;54(4):217-23.
 33. Bootsma-van der Wiel A, Gussekloo J, De Craen AJM, Van Exel E, Bloem BR, Westendorp RGJ. Walking and Talking as Predictors of Falls in the General Population: The Leiden 85-Plus Study. *J Am Geriatr Soc*. 2003;51(10):1466-71.
 34. Latt MD, Lord SR, Morris JGL, Fung VSC. Clinical and Physiological Assessments for Elucidating Falls Risk in Parkinson's Disease. *Mov Disord*. Jul 15 2009;24(9):1280-9.
 35. Allcock LM, Rowan EN, Steen IN, Wesnes K, Kenny RA, Burn DJ. Impaired attention predicts falling in Parkinson's disease. *Parkinsonism Relat Disord*. Feb 2009;15(2):110-5.

36. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol.* 2000;41(1):49-100.
37. Brown RG, Marsden CD. Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. *Brain.* Feb 1991;114 (Pt 1A):215-31.
38. Wu T, Hallett M. Neural correlates of dual task performance in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry.* Jul 2008;79(7):760-6.
39. Ashburn A, Fazakarley L, Ballinger C, Pickering R, McLellan LD, Fitton C. A randomised controlled trial of a home based exercise programme to reduce the risk of falling among people with Parkinson's disease. *J Neurol Neurosurg Psychiatry.* Jul 2007;78(7):678-84.
40. Weerdesteyn V, Schillings AM, van Galen GP, Duysens J. Distraction affects the performance of obstacle avoidance during walking. *J Mot Behav.* 2003;35(1):53-63.
41. Hartmann A, Luzi S, Murer K, de Bie RA, de Bruin ED. Concurrent validity of a trunk tri-axial accelerometer system for gait analysis in older adults. *Gait Posture.* Apr 2009;29(3):444-8.

Chapter 5

Involvement of specific executive functions in mobility in Parkinson's disease

Katrijn Smulders, Marlies van Nimwegen, Marten Munneke,
Bastiaan Bloem, Roy Kessels, Rianne Esselink
Parkinsonism & Related Disorders 2013; 19(1):126-8

Abstract

Background: Postural instability and gait disorders (PIGD) in Parkinson's disease (PD) seem to be associated with executive dysfunction. We investigated which specific executive functions are associated with functional mobility in mildly affected PD patients.

Methods: Functional mobility (Timed Up&Go Test, TUG), PIGD score, (spatial) working memory, set shifting, response inhibition and response generation were assessed in a large cohort of 232 non-demented PD patients.

Results: Both performance on the TUG and PIGD score were weakly associated with working memory and response generation (semantic and phonemic fluency). TUG also correlated with semantic fluency when corrected for disease severity and age.

Conclusion: These results indicate that response generation and working memory are associated with (and possibly also causally related to) gait and balance deficits. In order to fully interpret gait and postural stability of PD patients in everyday situations, the role of impairments in working memory and response generation should be taken into account.

Introduction

Parkinson's disease (PD) is characterized by its motor features including gait difficulty and postural instability. Moreover, already in the early stages of PD some 20% of patients have mild cognitive impairment.¹ Because of the underlying neurodegenerative nature of PD, cognitive impairments are overall related to increased motor severity.² For example, the motor subtype with predominantly posture and gait disorders is a strong predictor of severe cognitive decline.³ However, associations between more specific aspects of cognitive function and motor impairments are less clear.²

With respect to cognitive domains, the executive functions are particularly affected in PD. Executive deficits can hamper activities in everyday life in PD for various reasons. First, activities of daily living can be affected directly because of an inability to organize, shift, monitor and play. In addition, executive dysfunction can impair daily-life performance more indirectly, via a detrimental effect on motor function. Specifically, there is increasing evidence to suggest that executive functions play an important role in gait and postural adjustments.⁴ For example, even healthy individuals without cognitive deficits reduce their walking speed and take smaller steps when they must perform a secondary cognitive task while walking, suggesting that executive or cognitive control is required for seemingly automatic functions like walking.

The results from such dual task studies have consistently shown effects on various gait variables, in particular walking speed, stride length and step-to-step variability. However, it has not been clarified which specific aspects of executive function are important in relation to impairments in gait and balance. Here, we aimed to further clarify the association between functional mobility (Timed Up&Go Test), posture instability and gait disorders (PIGD), and four main aspects of executive function: updating/working memory, set shifting, response inhibition, and response generation in a large cohort of non-demented PD patients.

Methods

Participants

Our study sample was a subsample of the ParkFit study population.⁵ Baseline assessment of cognitive functions and mobility measures are presented here. Inclusion criteria were PD (diagnosed according to the UK Brain Bank criteria), age between 40-75 years, a sedentary lifestyle, Hoehn & Yahr (H&Y) ≤ 3 , and Mini-Mental State Examination (MMSE) ≥ 24 . The study was approved by the regional

medical ethical committee (CMO region Arnhem-Nijmegen) and patients gave their written informed consent.

The present analysis is limited to patients who completed all executive function and mobility tests ($N=232$, 66% men, 64.4 ± 7.9 years). Mean Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score was 33.4 ± 9.1 and mean MMSE score was 28.1 ± 1.6 . Almost 80% of patients ($n=183$) was in H&Y stage 2; the other patients had HY stage 1 ($n=3$; 1%), 1.5 ($n=6$; 3%), stage 2.5 ($n=35$; 15%) or stage 3 ($n=5$; 2%). Most patients (47%) scored category 3 for their level of education (range 1 – no education to 6 – university).

Materials and Procedure

The Timed Up&Go (TUG) test was used as an index of *mobility*.⁶ In this test the patient has to stand up from a chair, walk 3 m at comfortable speed, turn 180°, walk back to the chair and sit down again. The sum score of items 27-30 of the UPDRS-III (arising from chair, posture, gait, postural stability) was used to calculate PIGD score.

Updating/working memory was examined using the Spatial Working Memory (SWM) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB).⁷ In this computerized task, participants have to search for a hidden token by clicking a number of boxes that are presented in a spatial layout. After finding a token, participants have to search for a new token that is hidden in one of the other boxes. Within-search errors occur if a participant returns to a previously 'opened' box within a search, whereas between-search errors occur if a participant returns to a box that already contained a token in a previous search. Also, a strategy index reflects the efficiency of the search path.

Set shifting was assessed using the Intradimensional/Extradimensional (ID/ED) Shifting Task from CANTAB.⁷ Here, participants have to learn a sorting rule by clicking stimuli that differ in different dimensions (shapes and lines) using feedback. After six consecutive correct responses according to the to-be-learned rule, the rule changes and participants have to learn the new sorting rule. Outcome measures were the number of stages completed and the number of errors made (adjusted for the number of stages completed).

Response inhibition was measured using an auditory Stroop paradigm,⁸ which allowed for precise recording of reaction times per response (in contrast to the widely-used paper-and-pencil Stroop Color-Word Test). In this task, patients hear the words "high" or "low" spoken at a high or low tone, every 2 sec. Participants were instructed to respond as fast as possible by repeating the tone of the stimulus. Verbal reaction time and accuracy were combined in a composite score (accuracy/verbal reaction time).

Response generation was measured by the ability to access long-term memory using either a phonological cue (letter fluency; naming as many words as possible starting with the letter “M” in one minute) or a semantic cue (semantic fluency; naming as many animals in one minute).⁹

Individual performance on SWM, ID/ED and fluency were compared to age and/or education or IQ corrected available normative data for the CANTAB (n=2000)¹⁰ and the fluency tests (n=1856).⁹ An individual performance was classified as impaired if the individual score was more than 1.65 SD below the normative mean (i.e., below the 5th percentile).¹¹ No normative data were available for the Stroop paradigm.

Data analysis

To test the associations between performance on the TUG and PIGD score and the performance on cognitive tests, univariate regression coefficients were calculated using linear regression. Next, a multivariate linear regression model was constructed to predict TUG and PIGD using the significant variables from the univariate regression together with age, UPDRS-III score and educational level as independent variables. Significant contribution was accepted at $p < 0.05$.

Results

PD patients needed on average 9.51 ± 2.85 s to complete the TUG. Mean PIGD score was $2.3 (\pm 1.3)$. Regression coefficients for the association between fluency tests and the TUG were significant, yet weak (beta between -0.198 and -0.340, Table 1). Similar beta values were observed for the association between Spatial Working Memory and the TUG regarding between-search errors and strategy. Other cognitive outcome measures were not correlated with the TUG. The linear regression analysis with PIGD score as dependent variable produced similar results.

A stepwise multivariate regression model was constructed by entering fluency tests and SWM between errors and strategy scores, together with UPDRS-III score, age and educational level. UPDRS-III (beta = 0.263, $p < 0.001$), age (beta = 0.212, $p = 0.001$), and semantic fluency (beta = -0.197, $p = 0.002$) contributed significantly to the model, together explaining 24% of the total variance of the TUG. Only UPDRS-III (beta = 0.469, $p < 0.001$) and age (beta = 0.186, $p = 0.002$) survived multivariate regression with PIGD as dependent variable. This model explained 31% of the total variance of PIGD score.

Table 1. Cognitive test performance and univariate regression analysis for prediction of TUG and PIGD

Test (N=232)	Outcome measure	Test performance		Univariate regression with TUG ³		Univariate regression with PIGD ⁴	
		Mean ± SD	% impaired ⁵	Beta	SE	Beta	SE
Updating/Working Memory							
SWM ¹	Within-search errors	2.91 ± 4.36	4	0.032	0.043	0.196*	0.019
	Between-search errors	43.37 ± 20.97	4	0.274*	0.009	0.271*	0.004
	Strategy	35.63 ± 5.41	4	0.206*	0.034	0.137*	0.015
Set shifting							
ID/ED ²	Stages completed	7.52 ± 2.00	17	-0.041	0.094	-0.098	0.041
	Total errors (adjusted)	54.87 ± 46.14	18	0.051	0.004	0.106	0.002
Inhibition							
Auditory Stroop	Composite score	1.48 ± 1.72	NA	0.049	0.109	0.009	0.048
Response generation							
Fluency	Phonemic	11.51 ± 4.66	6	-0.198*	0.040	-0.142*	0.018
	Semantic	18.00 ± 5.71	26	-0.340*	0.031	-0.224*	0.014

¹ Spatial Working Memory; ² Intradimensional/Extradimensional Shifting task; ³ Timed Up&Go Test; ⁴ Postural Instability and Gait Disorders; ⁵ Impaired performance was defined as more than 1.65 SD deviation below the normative mean. For the auditory Stroop test, no normative values were available.
* Significant regression coefficients (p<0.05)

Discussion

In this study, we evaluated which of the four domains of executive function is involved in functional mobility in a large cohort of patients with PD. Spatial working memory and verbal fluency showed small but significant associations with both the TUG and PIGD scores. Moreover, semantic fluency was significantly associated with mobility, independent of age and severity of motor signs as measured with the UPDRS-III.

The association of response generation and working memory (updating) with the TUG can be explained as an involvement of executive control during this seemingly pure motor task. Ongoing movement requires continuous monitoring and updating in order to adjust to ongoing changes in the environment. Specifically, the turning and transfer components of the TUG might demand executive processing. Alternatively, one could argue that processing speed underlies both executive functions and the TUG.¹² However, the Stroop task is presumably the most time-critical cognitive task in our design, but was not associated with performance on the TUG.

It is important to note that the patients in our sample were relatively mildly affected. The H&Y stages and UPDRS-III scores were low. This indicates that our research sample of PD patients probably had only minor gait difficulties and postural instability. With regard to the extent of executive dysfunction, impairments were present in set shifting (17-18%) and semantic fluency (26%), but not in working memory and phonemic fluency. However, even small decrements in executive function may affect motor function in more complex daily-life environments, which require more planning and switching than the TUG test which was performed under well-controlled circumstances in our study. Also, since PD progressively affects both cognitive and motor functions, the interaction between both domains might place PD patients in vulnerable everyday situations in more advanced disease stages.

The results from this study revealed that in non-demented PD patients with minor gait deficits, response generation and working memory are the executive functions that are weakly associated with functional mobility. With regard to clinical practice, we recommend that in order to fully interpret gait and postural stability of PD patients in everyday situations, the role of impairments in working memory and response generation, even when mild, should be taken into account.

References

1. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*. 2009;72(13):1121-6.
2. Green J, McDonald WM, Vitek JL, et al. Cognitive impairments in advanced PD without dementia. *Neurology*. 2002;59(9):1320-4.
3. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*. 2006;77(5):585-9.
4. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329-42.
5. Van Nimwegen M, Speelman AD, Smulders K, et al. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. *BMC Neurol*. 2010;10:70.
6. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-8.
7. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia*. 1994;5(5):266-81.
8. Cohen G, Martin M. Hemisphere differences in an auditory Stroop test. *Percept Psychophys*. 1975;17(1):79-83.
9. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc*. 2006;12(1):80-9.
10. Robbins TW, James M, Owen AM, et al. A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *J Int Neuropsychol Soc*. Sep 1998;4(5):474-90.
11. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4th. New York: Oxford University Press; 2004.
12. McDowd J, Hoffman L, Rozek E, et al. Understanding Verbal Fluency in Healthy Aging, Alzheimer's Disease, and Parkinson's Disease. *Neuropsychology*. Mar 2011;25(2):210-25.

Chapter 6

Trait impulsivity is associated with the risk of falls in Parkinson's disease

Katrijn Smulders, Rianne Esselink, Roshan Cools, Bastiaan Bloem

PLoS One 2014;9(3):e91190

Abstract

Background: Impulsivity is a “tendency to act prematurely without foresight.” Clinical experience suggests that such impulsive behavior can impact on the fall risk in Parkinson’s disease (PD), but this has never been tested. We investigated whether trait impulsivity is related to fall risk in a large cohort of PD patients. We also investigated whether trait impulsivity affects the fall risk differently for patients with more or less postural instability and gait disability (PIGD).

Methods: 388 patients with PD ($H\&Y\leq 3$) completed the Barratt Impulsiveness Scale (BIS-11, higher scores indicating greater impulsivity) to assess trait impulsivity, including three subscales: motor impulsivity (e.g. “I do things without thinking”), attentional impulsivity (e.g. “I concentrate easily”) and non-planning (e.g. “I plan tasks carefully”). Falls were registered prospectively for 6 months. Patients classified as non-fallers (0 falls, $n=237$) were compared to recurrent PD fallers (>1 fall, $n=78$).

Results: Total impulsivity scores were higher for recurrent fallers (59.5) compared to non-fallers (56.8; $p=.012$). This effect was predominantly driven by higher scores on the subscale for attentional impulsivity ($p=.003$). The difference in attentional impulsivity was independent of gender, disease severity, dopaminergic medication, and cognitive function. Motor and non-planning impulsivity did not differ between recurrent fallers and non-fallers. There was no evidence that impulsivity modulated the association between PIGD and fall risk.

Conclusion: This is the first evidence that impulsivity, in particular in the attentional domain, is related to fall risk in PD.

Introduction

Falls in Parkinson's disease (PD) are common and incapacitating.¹ Considering the hallmark motor symptoms of PD, the high fall rate is understandable. However, not all patients with postural instability or gait disability fall, perhaps because these patients compensate by moving more cautiously. In contrast, frequent fallers might miss such adaptive behavior, perhaps due to lack of insight or impulsivity.² Indeed, Ahlskog stated that "...some of the worst fallers are those who impulsively jump from their chair or turn without thinking".³ Quinn coined the term "motor recklessness" to describe such behavior, which is common in patients with progressive supranuclear palsy.⁴ There is as yet, however, no quantitative proof for this clinical observation.

Impulsivity is a complex concept, including "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes".⁵ Our primary aim was to investigate whether trait impulsivity is associated with fall risk in PD patients. To this end, we assessed trait impulsivity using the Barratt Impulsiveness Scale 11 (BIS-11) to assess the personality construct of impulsivity. The BIS-11 distinguishes motor impulsivity ("acting without thinking")⁶, attentional impulsivity (a lack of "focusing on the task at hand" and "thought insertions and racing thoughts")⁷, and non-planning impulsivity (a lack of "futuring or forethought").^{6,7} Fall incidents were prospectively monitored for a period of six months in a large cohort of PD patients. As a second aim, we investigated whether trait impulsivity modulates the association between postural instability and gait disability and fall risk.

Methods

Ethics statement

This study was approved by the regional medical ethics committee (CMO region Arnhem-Nijmegen). Written informed consent was obtained from all participants before the first assessment.

Participants

The included patients are a subset of the 586 PD patients who participated in the ParkFit study, a multicentre, randomized clinical trial that evaluated the effectiveness of a behavioral program to promote physical activity.⁸ Eligibility criteria in the ParkFit study were PD according to the UK Brain Bank criteria,⁹ Hoehn and Yahr (H&Y) ≤ 3 ,¹⁰ age between 40 and 75 years, and a sedentary lifestyle. Exclusion criteria were: unclear diagnosis (no gratifying, sustained

response to dopaminergic therapy), Mini-Mental State Examination (MMSE) <24,¹¹ unable to complete Dutch questionnaires, severe co-morbidity, daily institutionalized care, and deep brain surgery.

After exclusion of participants who had no (n=124) or incomplete BIS-11 questionnaires (n=16), or incomplete fall records (n=58), 388 participants were included. There were no significant differences between included and excluded patients with regard to demographic (age, gender, educational level) and disease characteristics (H&Y stage, MMSE). Because recurrent falls are generally viewed as indicative of pathology, whereas single falls can be regarded as occasional falls with uncertain clinical relevance,¹²⁻¹⁴ we excluded all patients with a single fall over 6 months (n=73) for the primary analysis (see *Falls*). This resulted in a sample of 315 patients (66% men, 65 ± 8 years). Mean Unified Parkinson's Disease Rating Scale-III (UPDRS-III) was 33 ± 10, 76% were in H&Y stage 2 (H&Y 1: 2; H&Y 1.5: 3%; H&Y 2.5: 16%; H&Y 3: 5%), and mean MMSE score was 28 ± 2 (Table 1).

Table 1. Demographic and clinical measures for fall groups

	Non-fallers	Recurrent fallers	p value
N	237	78	
Age	65 ± 8	65 ± 8	.715
Gender (% M)	69%	56%	.046
Hoehn & Yahr (%)			
1	1%	3%	
1.5	3%	1%	
2	80%	63%	.001
2.5	14%	20%	
3	2%	13%	
UPDRS-III	32 ± 10	37 ± 11	<.001
PIGD	2.6 ± 1.6	3.5 ± 1.7	<.001
MMSE	28 ± 2	28 ± 2	.097
Falls	0	5 ± 7	<.001
LED total	432 ± 399	634 ± 478	<.001
% using DA agonists	51%	65%	.027
LED-agonists	123 ± 226	164 ± 163	.137
Physical activity level (hours/week)	15.6 ± 10.7	17.3 ± 10.7	.227

P values of independent t-tests and chi-square are presented to compare fall groups. UPDRS-III: Unified Parkinson's Disease Rating Scale motor examination; PI GD: Postural Instability and Gait Disability; MMSE: Mini-Mental State Examination; LED: Levodopa Equivalent Dose. DA: dopamine.

Items 27-30 of the UPDRS-III (arising from chair, posture, gait, postural stability) were summed to calculate PIGD scores of the participants. Total levodopa dose equivalent (LED) was calculated, pooling different drugs according to the following formula: regular levodopa dose \times 1 + slow release levodopa \times 0.7 + bromocriptine \times 10 + apomorphine \times 10 + ropinirole \times 20 + pergolide \times 100 + pramipexole \times 100 + [regular levodopa dose + (slow release levodopa \times 0.7)] \times 0.2 if taking entacapone.¹⁵ LED values for dopamine agonists (LED-agonists) were calculated using the same formula excluding the levodopa factors.

The level of physical activity level was assessed with the LASA physical activity questionnaire (LAPAQ), a validated seven day recall of physical activities.¹⁶

Cognitive assessment

All participants completed a cognitive test battery to assess attentional set switching (CANTAB intra-extra dimensional set shift (IDED)), spatial working memory (CANTAB SWM test), and verbal fluency (letter fluency).^{17,18}

Trait impulsivity

The Dutch version of the Barratt Impulsiveness Scale 11 is a self-report instrument to assess the personality construct of impulsivity.^{7,19} The questionnaire consists of 30 items that are scored on a four point scale (1-4) and that taps into three sub-traits: motor impulsivity (e.g. “*I do things without thinking*”), attentional impulsivity (e.g. “*I concentrate easily*”), and non-planning impulsivity (e.g. “*I plan tasks carefully*”). Total impulsivity is calculated as the sum of all items. Higher scores on the BIS-11 indicate greater impulsivity. Previous studies have shown adequate internal consistency with Cronbach’s α of 0.81 in a study using the Dutch BIS-11.²⁰ Cronbach’s α of the total BIS score in the present study was 0.75. Cronbach’s alpha for attentional BIS was 0.67, for non-planning BIS 0.63 and for motor BIS 0.38.

Falls

Falls were registered monthly using an automated system to monitor falls by telephone (Falls Telephone, ASK Community Systems). The Falls Telephone called participants every month and asked them how many times they had fallen in the previous month. The Falls Telephone is a reliable instrument to monitor falls in PD (sensitivity: 100%, specificity: 78%).²¹ All fall entries were verified by a personal telephone call of trained research assistants to further increase specificity. A fall was defined as “an unexpected event in which the participant comes to rest on the ground, floor, or lower level”.²² To illustrate, falling back

in a chair when trying to stand up from a chair was not characterized as a fall, whereas standing upright in front of a chair, losing balance and falling into a chair, was counted as a fall. Participants were classified as non-faller (0 falls over 6 months), single faller (1 fall over 6 months) and recurrent faller (>1 fall over 6 months). These groups differed significantly with regard to UPDRS-III ($p<.001$), H&Y ($p=.002$) and PIGD ($p<.001$). Compared to the non-fallers, single fallers had significantly higher UPDRS-III ($p=.032$) and PIGD scores ($p=.041$), but did not have different H&Y stages ($p=.809$). Compared to the recurrent fallers, single fallers had lower H&Y ($p=.002$) and PIGD scores ($p=.0049$), but these groups did not differ with regard to UPDRS-III scores ($p=.137$).

Statistical analysis

Statistical tests on demographic, clinical, cognitive and impulsivity outcomes were carried out comparing non-fallers with recurrent fallers. Independent samples t-tests were used for continuous variables, and Chi-square tests for categorical variables. Effect size was calculated using Cohen's d for the difference between non-fallers and recurrent fallers in case of significant differences on impulsivity measures. In an additional analysis, we included the single fallers in the group of non-fallers (non-recurrent fallers, ≤ 1 falls) and compared impulsivity scores of this group with the group of recurrent fallers (>1 falls).

To account for the possible contribution of gender, disease severity (H&Y and PIGD), and dopaminergic medication (LED total and LED-agonists) on impulsivity or fall risk, we constructed four multivariate logistic regression models (forced entry) with fall group (non-fallers vs. recurrent fallers) as the dependent variable. In model 1, total impulsivity and gender were included as independent factors. In model 2 total impulsivity, H&Y and PIGD scores were included as independent factors. In model 3 total impulsivity, LED total and LED-agonists were the independent factors. Finally, we investigated whether fall risk was predicted by impulsivity independent of cognitive function. In this fourth model we added the cognitive tests that were significantly different between fall groups and MMSE score as independent factors together with total impulsivity. These analyses were repeated replacing total impulsivity with subscales that were significantly different between non-fallers and recurrent fallers.

To assess whether impulsivity modulated the effect of PIGD on fall risk, a logistic regression analysis (forced entry method) was applied with fall group as dependent variable, and the interaction term total impulsivity \times PIGD, total impulsivity and PIGD as independent variables. The independent factors were centered to facilitate the interpretation of the coefficients. This analysis was repeated with subscales that were significantly different between non-fallers

and recurrent fallers instead of total impulsivity. Significance was accepted at $p < .05$ for all analyses.

Results

Demographic and clinical differences between fall groups (Table 1)

Seventy-eight (25%) participants reported more than one fall in the period of six months. Non-fallers and recurrent fallers were comparable with regard to age and MMSE scores (all p 's $> .1$). Women were more likely to report recurrent falls ($p = .046$). Compared to non-fallers, recurrent fallers had higher H&Y stages ($p = .001$) and higher UPDRS-III and PIGD scores (p 's $< .001$). Regarding dopaminergic medication, recurrent fallers had higher LED values than non-fallers (p 's $< .001$). Although the percentage of recurrent fallers using dopamine agonists was higher than that of non-fallers ($p = .027$), the groups did not differ in LED-agonists ($p = .137$). Recurrent fallers and non-fallers had comparable levels of physical activity ($p = .227$).

Impulsivity and fall risk

Patients with PD who experienced multiple falls scored 2.7 points higher on the total BIS-11 than non-fallers ($t_{1,313} = -2.54$, $p = .012$, Table 2). Of the subscales, only attentional impulsivity was different between recurrent fallers and non-fallers, with 1.2 higher impulsivity scores for the fallers ($t_{1,313} = -2.83$, $p = .005$). Effect sizes were small to medium; Cohen's d was 0.33 for total impulsivity and 0.37 for attentional impulsivity. Motor impulsivity ($t_{1,313} = -1.22$, $p = .225$) and non-planning ($t_{1,313} = -1.66$, $p = .098$) did not differ between fall groups.

In an additional analysis we compared impulsivity scores of non-recurrent fallers (consisting of the non-fallers and single fallers) with those of recurrent fallers. The results of this analysis were similar to the primary analysis: Recurrent fallers had higher total ($t_{1,386} = -2.33$, $p = .020$) and attentional impulsivity scores ($t_{1,386} = -2.42$, $p = .016$) than non-recurrent fallers. The groups did not differ on motor ($t_{1,386} = -1.28$, $p = .203$) and non-planning impulsivity ($t_{1,386} = -1.57$, $p = .116$).

Table 2. Self-reported impulsivity scores (BIS-11) for fall groups

	Non-fallers	Recurrent fallers	T	P value	Cohen's d
Total impulsivity	56.8 ± 8.3	59.5 ± 8.0	-2.54	.012	0.33
Motor impulsivity	18.1 ± 2.8	18.5 ± 2.6	-1.22	.225	-
Attentional impulsivity	14.5 ± 3.4	15.7 ± 3.7	-2.83	.005	0.37
Non-planning	24.3 ± 4.7	25.3 ± 4.6	-1.66	.098	-

P values are presented for comparisons between fall groups using the independent samples t-test. Cohen's d indicates effect size (0.2: small effect; 0.5: medium effect; 0.8: large effect).

Controlling gender, disease severity, and dopaminergic medication

We constructed multivariate regression models to assess whether impulsivity contributed to recurrent fall risk independently of gender, disease severity, and dopaminergic medication (Tables 3 and 4). These analyses showed that total impulsivity was an independent predictor of fall risk when gender and disease severity were controlled, with an odds ratio of 1.04 (95% CI: 1.03-1.08 controlling gender; 95% CI: 1.03-1.07 controlling disease severity). In contrast, total impulsivity was not an independent predictor for fall risk when dopaminergic medication was controlled.

Attentional impulsivity was a consistent, independent contributor to fall risk in all regression models with odd's ratios between 1.09-1.11 (95% CI: 1.03-1.19 controlling gender or disease severity; 95% CI: 1.00-1.18 controlling medication). Other significant contributors to fall risk were PIGD (in model with total BIS: OR: 1.31, 95% CI: 1.08-1.60; in model with attentional BIS: OR: 1.31, 95% CI: 1.07-1.59) and LED total (in model with total BIS: OR: 3.10, 95% CI: 1.45-6.64; in model with attentional BIS: OR: 3.06, 95% CI: 1.42-6.57).

Cognitive function

There were no significant differences between recurrent and non-fallers on the cognitive tests assessing attentional set shifting and spatial working memory (p 's > .08; Table 5). Recurrent fallers scored significantly lower on verbal fluency compared with non-fallers (p = .042). However, logistic regression demonstrated that total BIS (OR: 1.04, 95% CI: 1.01-1.08) and attentional BIS (OR: 1.11, 95% CI: 1.03-1.20) remained independent significant predictors for fall risk when controlled for letter fluency performance and MMSE score (Tables 3 and 4).

Table 3. Output parameters of multivariate logistic regression models assessing the association between total impulsivity and fall risk

	Controlled variable				Total impulsivity			Model
	B (SE)	OR	95% CI	B (SE)	OR	95% CI	R2 (Nagelkerke)	
Controlling:								
1. Gender	NS			0.04 (0.02)	1.04	1.01-1.07	0.05	
2. Disease severity								
H&Y	NS			0.04 (0.02)	1.04	1.01-1.08	0.13	
PIGD	0.27 (0.10)	1.31	1.08-1.60					
3. Medication ^a								
LED total	1.13 (0.38)	3.10	1.45-6.64	NS			0.07	
LED-agonists	NS							
4. Cognitive function								
MMSE	NS			0.04 (0.02)	1.04	1.01-1.08	0.05	
Verbal fluency	NS							

Output of logistic regression models controlling for gender, disease severity, dopaminergic medication, and cognitive function. H&Y: Hoehn and Yahr stages. PI GD: Postural instability and gait disability. MMSE: Mini-Mental State Examination. LED: levodopa dose equivalent. ^a LED values were divided by 1000 for these analyses.

Table 4. Output parameters of multivariate logistic regression models assessing the association between attentional impulsivity and fall risk

Controlling:	Controlled variable			Attentional impulsivity			Model
	B (SE)	OR	95% CI	B (SE)	OR	95% CI	
1. Gender	NS			0.10 (0.04)	1.11	1.03-1.19	0.05
2. Disease severity							
	NS			0.10 (0.04)	1.11	1.03-1.19	0.14
	0.27 (0.10)	1.31	1.07-1.59				
3. Medication							
	1.12 (0.38)	3.06	1.42-6.57	0.09 (0.04)	1.09	1.00-1.18	0.08
	NS						
4. Cognitive function							
	NS			0.10 (0.04)	1.11	1.03-1.20	0.06
	NS						

Output of logistic regression models controlling for gender, disease severity, dopaminergic medication, and cognitive function. H&Y: Hoehn and Yahr stages. PIGD: Postural instability and gait disability. MMSE: Mini-Mental State Examination. LED: levodopa dose equivalent. a LED values were divided by 1000 for these analyses.

Table 5. Cognitive assessment for fall groups

		Non-fallers	Recurrent fallers	P value
Attentional set switching	IDED Adjusted errors	52 ± 46	61 ± 49	.168
	IDED Stages completed	8 ± 2	7 ± 2	.201
Spatial working memory	SWM Between errors	41 ± 21	46 ± 21	.083
	SWM Within errors	3 ± 4	3 ± 4	.944
Verbal fluency	Score letter fluency	12 ± 4	11 ± 4	.046

Mean (sd) values for performance on cognitive tests assessing attention, working memory and fluency are compared between fall groups. IDEDED: Intra- and extradimensional set shift test. SWM: Spatial working memory

Impulsivity, PIGD, and fall risk

To assess whether impulsivity has a larger effect on fall risk for patients with more gait and balance problems, a logistic regression model with independent factors total impulsivity \times PIGD, total impulsivity and PIGD, and fall group as dependent factor was constructed. Total impulsivity \times PIGD was not an independent predictor of fall risk in this model ($p < .239$). Additionally, we tested the interaction between subscale attentional impulsivity and PIGD as a predictor for fall risk in a similar model. This interaction term was also not a significant predictor of fall risk when the main effects were controlled ($p = .348$).

Discussion

The present data suggest that trait impulsivity is associated with the risk of falls for patients with PD. Patients who sustained multiple falls within 6 months reported higher impulsivity than non-fallers. In particular, fallers scored higher on attentional impulsivity, although the effect size was small to medium. This difference was independent of gender, disease severity, amount of dopaminergic medication use, and cognitive function. We did not find evidence that impulsivity influenced fall risk differently in patients with high or low PIGD scores.

Attentional impulsivity reflects a tendency to be more sensitive to distraction.^{7,19} If a patient cannot adequately devote attention to gait and postural stability, and is susceptible to distraction, then this likely challenges stability. Hence, an alternative account for our findings is that impaired attention underlies differences between fall groups rather than impulsivity. Indeed, difficulty with sustained attention has been associated with fall risk in PD before,²³ and in the current study recurrent fallers scored lower on a test of verbal fluency than non-fallers. To rule out the possibility that attentional deficits could explain our

findings, we controlled for differences on this cognitive test and found that the association between impulsivity and fall risk was independent of attentional functions. This finding is in line with a previous study of our group showing that attentional demands operationalized in a dual task paradigm could not explain fall risk in PD.²⁴ Moreover, in a study of healthy young subjects, the BIS-11 was found to correlate with performance on a neuropsychological test assessing impulsivity, but not with a measure of sustained attention.²⁵ Hence, our findings suggest that impulsive behavior of the recurrent fallers represents a different construct than attentional deficits.

Based on prior work,^{26,27} motor impulsivity was the most likely candidate to correlate with falls. This aspect of impulsivity reflects the inability to control prepotent, impulsive actions.²⁸ The only other study evaluating impulsivity and fall risk reported that stroke patients with a history of falls performed more poorly on a task assessing motor impulsivity (bilateral scanning task).²⁶ The idea that falling in PD might be related to motor impulsivity came from another study demonstrating that PD patients with predominantly postural instability and gait disability tended to make more impulsive errors in a computerized lab tests (Simon task) compared with tremor-dominant patients.²⁷ The authors suggested that motor impulsivity in combination with PIGD symptoms makes PD patients extra vulnerable for falls. Our results generally concur with this suggestion. However, impulsivity, whether self-reported or measured with computerized tests in the lab, is well known to be a multifactorial phenomenon.^{29,30} Here we extend this prior work by showing that fall risk is particularly associated with self-reported attentional rather than motor impulsivity. Whether this effect of self-reported attentional impulsivity extends to attentional impulsivity as measured with laboratory computer tests, e.g. in terms of premature responding on a 5 choice task, remains to be determined.

We had expected that impulsive behavior would mainly be risky for patients with greater postural instability and gait disability. However, our findings were not consistent with this hypothesis. We observed that impulsivity increased fall risk for patients with both higher and lower PIGD scores, evidenced by a non-significant contribution of the impulsivity \times PIGD interaction term to fall risk. To illustrate the impact of impulsivity, patients with high impulsivity scores (total or attentional) were 1.7 times as likely to fall compared with patients with low impulsivity scores (OR for an interquartile range increase). These findings suggest that impulsive tendencies need consideration in the clinic, even in patients who present with minor axial impairments.

We considered the role of dopaminergic medication, because dopamine replacement therapy, and particularly dopamine agonist dosage, is associated

with impulse control disorders (ICD) in PD.³¹⁻³³ Moreover, the fallers in our study were on a higher dose of dopamine, presumably because of their greater disease severity. Theoretically, this could mean that higher disease severity caused falls and, in parallel, called for more dopaminergic medication, thereby increasing impulsivity. To falsify this explanation, we controlled for dosage of dopaminergic medication, dosage of dopamine agonists and disease severity in our analysis, and this did not change the finding that attentional impulsivity was higher in recurrent fallers compared to non-fallers. However, the addition of total LED values resulted in non-significant associations between total impulsivity and fall risk. Hence, the role of dopamine in impulsive behavior and fall risk needs to be further explored.

The patients of our cohort had to have a sedentary lifestyle in order to be eligible for the study and were in the early to moderate stages of PD. This selection limits generalization to the general PD population. Nevertheless, falls were common in this cohort. This stresses the need to improve identification of patients who are at risk for falls, preferably before the first fall. A second limitation is the use of the BIS questionnaire. The BIS-11 has not yet been validated in a cohort of PD patients. Moreover, we found that the motor BIS had low internal consistency. Validation of the total BIS and its subscales in an independent cohort, representative of the general PD population is therefore warranted. Finally, in a recent study it was found that PD patients with ICD's score higher on attentional BIS, but not on total BIS, than the ICD negative patients.³⁴ Extending this finding to our study would suggest that our recurrent fallers might be more at risk for ICD's. In that regard, it would have been interesting to document ICD's in our cohort as another dimension of impulsivity. However, the absence of information on ICD status in our cohort does not diminish the validity of our interpretations with regard to the relation between trait impulsivity and falls.

The present study provides the first evidence that trait impulsivity is associated with fall risk in PD. However, impulsivity is a complex multifactorial phenomenon.³⁰ Future research is needed to further explore different aspects of impulsive behavior in relation to fall risk (see ²⁹ for a theoretical framework).

References

1. Pickering RM, Grimbergen YA, Rigney U, et al. A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov Disord.* Oct 15 2007;22(13):1892-900.
2. Bloem BR, Bhatia KP. Gait and balance in basal ganglia disorders. In: Bronstein AM, Brandt T, Nutt JG, Woollacott MH, eds. *Clinical Disorders of Balance, Posture and Gait.* London: Arnold; 2004:173-206.
3. Ahlskog JE. Think before you leap Donepezil reduces falls? *Neurology.* Oct 5 2010;75(14):1226-7.
4. Bloem BR, Munneke M, Mazibrada G, et al. The nature of falling in progressive supranuclear palsy. *Mov Disord.* 2004;19(3):359-60.
5. Daruna JH, Barnes PA. A neurodevelopmental view of impulsivity. In: McCown WG, Johnson JL, Shure MB, eds. *The impulsive client: Theory, research, and treatment.* Washington, DC, US: American Psychological Association; 1993:23-37.
6. Barratt ES. Impulsiveness subtraits: Arousal and information processing. In: Spence JT, Izard CE, eds. *Motivation, emotion and personality.* North Holland Elsevier Science Publishers; 1985:137-46.
7. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol.* 1995;51(6):768-74.
8. Van Nimwegen M, Speelman AD, Smulders K, et al. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. *BMC Neurol.* 2010;10:70.
9. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* Mar 1992;55(3):181-4.
10. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;17(5):427-42.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-98.
12. Anstey KJ, Wood J, Kerr G, Caldwell H, Lord SR. Different cognitive profiles for single compared with recurrent fallers without dementia. *Neuropsychology.* Jul 2009;23(4):500-8.
13. Holtzer R, Friedman R, Lipton RB, Katz M, Xue X, Verghese J. The relationship between specific cognitive functions and falls in aging. *Neuropsychology.* Sep 2007;21(5):540-8.
14. Mak MK, Pang MY. Parkinsonian single fallers versus recurrent fallers: different fall characteristics and clinical features. *J Neurol.* Sep 2010;257(9):1543-51.
15. Esselink RA, de Bie RM, de Haan RJ, et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. *Neurology.* Jan 27 2004;62(2):201-7.
16. Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P. Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. *J Clin Epidemiol.* Mar 2004;57(3):252-8.

17. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia*. 1994;5(5):266-81.
18. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc*. 2006;12(1):80-9.
19. Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH. Fifty years of the Barratt Impulsiveness Scale: An update and review. *Pers Individ Diff*. 2009;47(5):385-95.
20. Goudriaan AE, Oosterlaan J, De Beurs E, Van Den Brink W. The role of self-reported impulsivity and reward sensitivity versus neurocognitive measures of disinhibition and decision-making in the prediction of relapse in pathological gamblers. *Psychol Med*. Jan 2008;38(1):41-50.
21. Van der Marck MA, Overeem S, Klok PC, Bloem BR, Munneke M. Evaluation of the falls telephone: an automated system for enduring assessment of falls. *J Am Geriatr Soc*. Feb 2011;59(2):340-4.
22. Lamb SE, Ferrucci L, Volapto S, Fried LP, Guralnik JM. Risk factors for falling in home-dwelling older women with stroke: the Women's Health and Aging Study. *Stroke*. 2003;34(2):494-501.
23. Allcock LM, Rowan EN, Steen IN, Wesnes K, Kenny RA, Burn DJ. Impaired attention predicts falling in Parkinson's disease. *Parkinsonism Relat Disord*. Feb 2009;15(2):110-5.
24. Smulders K, Esselink RA, Weiss A, Kessels RP, Geurts AC, Bloem BR. Assessment of dual tasking has no clinical value for fall prediction in Parkinson's disease. *J Neurol*. Feb 1 2012.
25. Keilp JG, Sackeim HA, Mann JJ. Correlates of trait impulsiveness in performance measures and neuropsychological tests. *Psychiatry Res*. Jun 30 2005;135(3):191-201.
26. Rapport LJ, Webster JS, Flemming KL, et al. Predictors of falls among right-hemisphere stroke patients in the rehabilitation setting. *Arch Phys Med Rehabil*. Jun 1993;74(6):621-6.
27. Wylie SA, van den Wildenberg W, Ridderinkhof KR, Claassen DO, Wooten GF, Manning CA. Differential susceptibility to motor impulsivity among functional subtypes of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Aug 23 2012.
28. Van den Wildenberg WP, Wylie SA, Forstmann BU, Burle B, Hasbroucq T, Ridderinkhof KR. To head or to heed? Beyond the surface of selective action inhibition: a review. *Frontiers in human neuroscience*. 2010;4:222.
29. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron*. Feb 24 2011;69(4):680-94.
30. Evenden JL. Varieties of impulsivity. *Psychopharmacology (Berl)*. Oct 1999;146(4):348-61.
31. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. *Arch Neurol*. Aug 2007;64(8):1089-96.
32. Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. *Brain*. May 2011;134(Pt 5):1438-46.

33. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. May 2010;67(5):589-95.
34. Antonini A, Siri C, Santangelo G, et al. Impulsivity and compulsivity in drug-naive patients with Parkinson's disease. *Mov Disord*. Feb 15 2011;26(3):464-8.

Chapter 7

Freezing of gait in Parkinson's disease is related to impaired motor switching during stepping

Katrijn Smulders, Rianne Esselink, Bastiaan Bloem, Roshan Cools

Submitted

Abstract

Background: Parkinson's disease has been associated with set switching difficulty in both the motor and the cognitive domain. However, the contribution of these set switching deficits to the primary motor symptoms of the disease is unclear. Here, we aimed to investigate whether set switching deficits contribute to gait and stepping problems in Parkinson's disease. By contrasting motor and cognitive set switching within the same paradigm, we elucidated the nature of the set switching deficit underlying freezing of gait.

Methods: We integrated step initiation with set switching within one task, and compared patients with and without freezing of gait with healthy subjects. Motor set switching was defined as a change in stepping direction from one trial to the next. Cognitive set switching was defined as a change in task rule (i.e. respond according to the shape or color of the presented stimulus).

Results: Patients with freezing of gait exhibited a set switching deficit at the motor level, but not at the cognitive level. There was no generic PD switch impairment.

Conclusion: These findings suggest that motor set switching deficits, commonly reported in tasks using verbal or tapping responses, extend to stepping and possibly contribute to the occurrence of freezing episodes.

Introduction

Disturbance of gait is a key feature of Parkinson's disease (PD) that severely restricts mobility. Already in the early stages of the disease, gait is impaired and episodes of freezing of gait (FOG) can occur. FOG poses a serious threat to balance and frequently results in falls.¹⁻⁴ The present study provides a mechanistic account of FOG in PD, by demonstrating an association with a set switching deficit during stepping. This observation concurs with the observation that FOG is predominantly triggered in situations that demand switching between motor actions, such as gait initiation.⁵

Switching deficits in the motor domain are core to PD.⁶⁻¹¹ This impairment has mainly been studied in tasks requiring a change within or between motor sequences. However, switching deficits are not confined to motor sets. In fact, a wealth of evidence indicates that PD patients lack the ability to flexibly switch between cognitive sets as well.^{9,12-16}

Thus, PD patients exhibit robust set switching deficits. Here we hypothesize that a set switching deficit might contribute to the occurrence of FOG. Consistent with this hypothesis, PD patients with FOG exhibited a set switching deficit on a well established neuropsychological test, the Trail Making Test B, which requires cognitive flexibility.¹⁷ This observation raises the interesting possibility that FOG reflects a deficit in cognitive set switching, in addition to or instead of a motor set switching deficit. However, cognitive and motor set switching have never been compared directly in patients with and without FOG.

In this study we compare PD patients with and without FOG and healthy subjects using a task that allows us to directly compare switching between cognitive sets with switching between motor sets. We chose to operationalize switching in terms of a task that requires actual stepping in order to maximize the ecological validity in the context of FOG.

Methods

Subjects

Fifty-one patients with Parkinson's disease (69% men, 59±7 years, 17±4 education years) were recruited from the outpatient centre of the Radboud University Nijmegen Medical Centre (Netherlands) and screened by a movement disorders specialist. Inclusion criteria were Parkinson's disease according to the UK Brain Bank Criteria,¹⁸ Hoehn & Yahr (H&Y) stage<3,¹⁹ and aged between 18 and 70 years. Exclusion criteria were global cognitive impairment (Mini Mental State Examination<24),²⁰ clinically relevant depression or anxiety disorders

according to DSM-IV,²¹ any visual or vestibular impairment or physical inability to perform the assessments, and inability to perform the task responding verbally. Twenty-two matched (age, gender, and years of education) healthy controls were recruited from the community (64% men, 60±6 years, 18±5 education years). Patients with PD performed the assessments after withdrawal of dopaminergic medication for at least 12 hours ("off" state).

All subjects gave their written informed consent for the study. The study was approved by our local ethics committee.

Clinical assessment

Severity of the disease was assessed in PD patients using the MDS-UPDRS-III (motor examination)²² and H&Y stages.¹⁹ The New Freezing of Gait Questionnaire (self-report)²³ was completed to identify patients with FOG (scores>0). Premorbid verbal intelligence was assessed with the National Adult Reading Test (NART, Dutch version).²⁴

To compare PD patients with FOG (PD-FOG), without FOG (PD-noFOG) and healthy subjects, three gender-, age-, and education-matched groups were made (n=14 for each subgroup). The PD-FOG group consisted of all patients with freezing of gait. The PD-noFOG group was matched with the PD-FOG group in terms of gender, age, and MDS-UPDRS-III score. Healthy subjects were matched with the PD-FOG group based on gender and age. Clinical and demographical parameters did not differ between groups (Table 1). Crucially, PD-FOG and PD-noFOG had comparable disease severity scores (MDS-UPDRS-III and H&Y).

Data collection

The subjects stood with each foot on one force plate recording ground reaction forces (sample rate: 1000 Hz). A monitor was placed in front of the participants at eye height. The stepping leg was determined by asking the subjects which foot they would use to kick a soccer ball.

Visual stimuli were generated in Matlab using the Psychophysics Toolbox extensions.²⁵⁻²⁷ The force plate data were recorded in Vicon Nexus, starting in synchrony with the presentation of the stimuli. All trials were recorded on video.

Simple reaction time

To obtain the simple reaction time (SRT) of stepping, subjects were instructed to step forward as soon as a blue cross was presented on the monitor. After five forward trials, five trials with a stepping backward instruction were conducted.

Table 1: Demographic and clinical characteristics of the participants (means and sd's).

	Total sample			Matched subgroups			
	PD	Controls	P	PD-noFOG	PD-FOG	Controls	P
N	51	22		14	14	14	
Age	59 (7)	60 (6)	0.791	60 (7)	58 (8)	59 (6)	0.764
Gender (%M)	69%	64%	0.677	64%	64%	64%	1.000
Education years	17 (4)	18 (5)	0.643	17 (3)	16 (5)	17 (5)	0.891
NART	105 (16)	112 (18)	0.068	106 (13)	103 (15)	115 (14)	0.064
MMSE	29 (1)			29 (1)	29 (1)		0.905 ¹
MDS-UPDRS-III	30 (13)			36 (10)	38 (12)		0.613 ¹
H&Y	1	1 (2%)		0	0		
	1.5	2 (4%)		0	0		
	2	36 (71%)		10 (71%)	7 (50%)		0.246 ¹
	2.5	12 (24%)		4 (29%)	7 (50%)		
NFOG-Q score				0 (0)	13 (6)		

NART: National Adult Reading Test; MMSE: Mini-Mental State Examination; MDS-UPDRS-III: Movement Disorders Society Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr stage; NFOG-Q: New Freezing of Gait Questionnaire

¹ P-value for the comparison between PD-noFOG and PD-FOG.

Set switching task (Figure 1 and 2)

On each trial, a colored shape was presented in the centre of the screen. This target was preceded by a word cue ('shape' [dutch: 'vorm'] or 'color' [dutch: 'kleur']) indicating whether subjects had to respond according to the color or shape of the target. Subjects were instructed to step forward if a cross (in the shape dimension) or yellow (in color dimension) target was presented, and step backward if a circle (in shape dimension) or blue (in color dimension) target was presented. The relevant dimension changed every second trial, so that subjects switched between color and shape task-sets on every second trial (AABBAA design). This cognitive set switching was manipulated in a manner that was orthogonal to the motor set switching manipulation. A motor set switch was defined as a change in stepping direction from one trial to the next. As such, the design provided us with four trial types (each 30 trials): (i) no switch trials (e.g. shape-cross after shape-cross trials), (ii) trials with a motor set switch but no cognitive set switch (motor switch trials; e.g. shape-cross after shape-circle trials), (iii) trials with a cognitive set switch but no motor set switch (e.g. shape-cross after color-yellow trials), and (iv) trials with both a motor and a cognitive

set switch (motor-cognitive set switch trials; e.g. shape-cross after color-blue trials). Because the shape and color of the stimulus could cue the same or a different step direction, there were congruent as well as incongruent trials.

The cue-target interval was 100 ms, thus preventing advance reconfiguration of the task-set and abolition of the presumed Parkinsonian set switching deficit.²⁸ The interval between the start of the response and the next cue depended on the time needed to execute a step derived from the simple reaction task (range: 1.5-3.3 s; Figure 2).

Data analysis

Force plate data were low-pass filtered at 10 Hz (4th order butterworth filter). Step onset was detected using an algorithm in Matlab and defined as the instant that the vertical ground reaction force was ~ 0 . Mean SRT's were calculated by subtraction of the stimulus onset from the step onset for each direction over four trials, excluding the first trial.

During the set switching task, the stepping direction of each trial was registered. In case of ambiguous registration, the video recording of the trial was checked afterwards. Incorrect trials and trials preceded by incorrect trials were excluded from further analyses of reaction times. Trials preceded by incorrect trials were also excluded from further analyses of accuracy. Reaction time was calculated for each switch condition by subtracting the stimulus onset from the step onset. Accuracy of stepping direction was calculated for each switch condition as the ratio of correct steps/number of trials.

Differences in demographic and clinical characteristics between PD patients and healthy subjects and between the three matched samples were statistically tested using independent t-tests and one-way ANOVA for continuous measures, and chi-square, Mann-Whitney U, and Kruskal-Wallis tests for categorical variables.

Reaction times and accuracy rates of the set switching task were analyzed using the general linear model with repeated measures (GLM-RM) with between-subject factor group with two levels (PD and controls) or subgroup with three levels (PD-FOG, PD-noFOG and healthy subjects). Within-subjects factors were cognitive switch (2 levels), motor switch (2 levels) and congruency (2 levels). Significant omnibus interaction effects were broken down using paired t-tests to assess within-group effects. SRTs were analyzed using similar GLM-RM with the within-subject factor direction (forward and backward).

For all analyses, significance was accepted at $p < .05$. Estimated marginal means and standard errors derived from the GLM-RM models are reported. Uncorrected means and standard error for each trial type are presented in Tables 2 and 3.

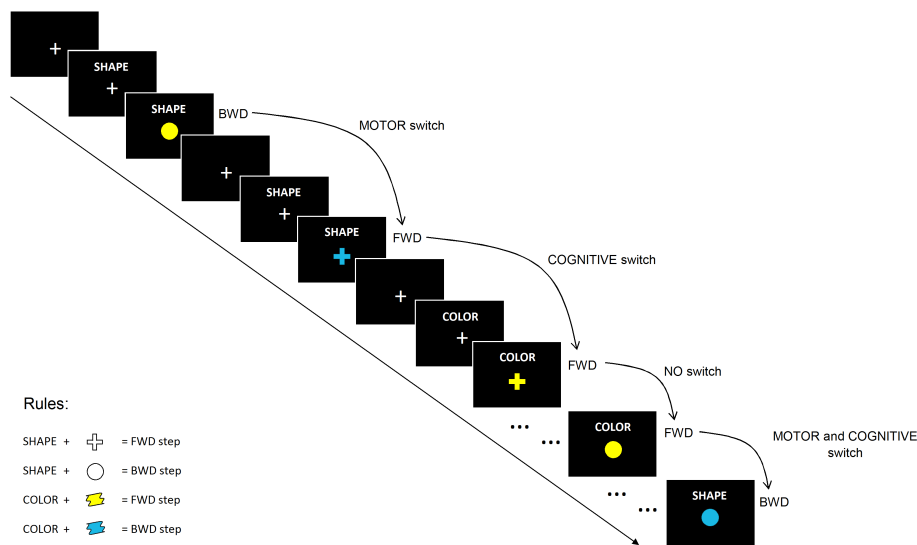


Figure 1. Example of sequence of stimuli of the set switching paradigm. A word cue indicated whether the 'shape' or 'color' rule should be followed. A colored shape cued a step forward (FWD) or backward (BWD). Motor switch: a change in stepping direction. Cognitive switch: a change in the relevant stimulus dimension.

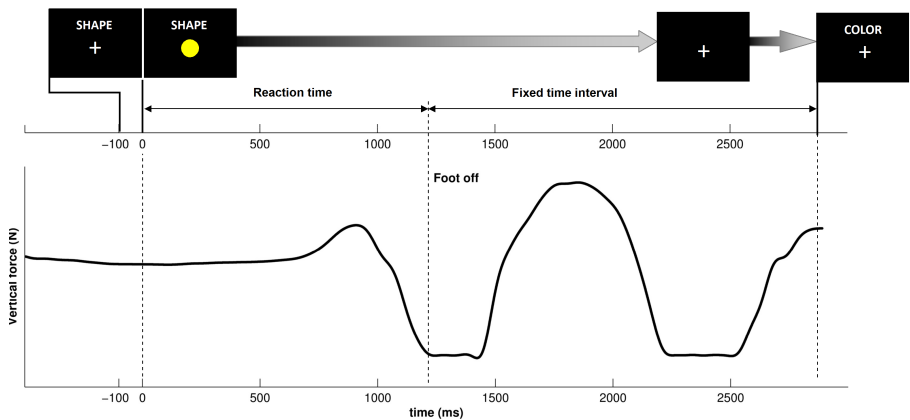


Figure 2. The timing of the set switching task in relation to ground reaction forces. Reaction time was calculated as the difference between instant of foot off (vertical force ~0) and the instant of stimulus presentation. A fixed time interval derived from the simple reaction task allowed sufficient time to return to the starting position.

Results

Set switching task

Effects of PD

PD patients responded significantly more slowly (1348 ± 47 ms) than healthy controls (1159 ± 72 ms) on the set switching task ($F_{1,71}=4.75$, $p=.033$), as evidenced by a main effect of group (PD versus controls). A motor switch did not significantly change reaction times (no main effect of motor switching: $F_{1,71}=0.11$, $p=.739$), whereas reaction times on trials with a cognitive switch were 113 ms longer than trials without a cognitive switch (main effect of cognitive switching: $F_{1,71}=141.44$, $p<.001$). PD patients did not show motor or cognitive switching deficits compared with healthy controls (no significant switch \times group effects). There was also no significant three-way interaction of cognitive switch \times motor switch \times group ($F_{1,71}=2.45$, $p=.122$, see Table 2).

PD patients did not make more errors than healthy subjects ($F_{1,71}=0.29$, $p=.595$). Errors were less common on motor switch than motor repeat trials (-1% , $F_{1,71}=8.79$, $p=.004$), but more common on cognitive switch than on cognitive repeat trials ($+1\%$, $F_{1,71}=7.63$, $p=.007$). This change in switch trials was not different between PD patients and controls (no significant switch \times group effects, $p's \geq .274$) and there was also no three-way interaction of cognitive switch \times motor switch \times group for accuracy ($F_{1,71}=1.69$, $p=.198$, Table 3).

Effects of FOG (Figure 3)

The PD-FOG group exhibited a significant motor switching deficit, as evidenced by a significant motor switch \times subgroup effect ($F_{2,39}=3.80$, $p=.031$). The reaction time difference between motor switch and repeat trials was 35 ms in PD-FOG ($t_{1,13}=-2.20$, $p=.047$), whereas there was no significant difference between these trial types in PD-noFOG and healthy subjects (both $p's \geq .168$). This motor switching deficit was seen in the context of intact cognitive switching. Thus, while a cognitive switch resulted in significantly slower stepping responses for all subgroups ($F_{1,39}=66.71$, $p<.001$), this effect was not different between subgroups (no cognitive switch \times subgroup effect: $F_{2,39}=0.17$, $p=.843$). In fact, the motor switching deficit was restricted to trials that did not also require a cognitive switch, as evidenced by a significant three-way interaction between cognitive switch \times motor switch \times subgroup ($F_{2,39}=3.51$, $p=.040$; Table 2).

These interaction effects were seen in the context of a main effect of subgroup, with reaction times being different between PD-FOG, PD-noFOG and controls ($F_{2,39}=3.50$, $p=.040$). Post-hoc analysis revealed that both PD-FOG and PD-noFOG responded more slowly than healthy controls ($p=.018$ and $p=.047$ respectively),

but reaction times did not differ between PD-FOG and PD-noFOG ($p=.671$).

The effects of motor and cognitive switching on accuracy rates did not differ between the three subgroups (no significant switch \times subgroups effects). The interaction between cognitive and motor switch was also not significantly different between the subgroups (no three-way interaction effect: $F_{2,39}=8.69$, $p=.427$, Table 3). There was also no main effect of subgroups in terms of accuracy across conditions ($F_{2,39}=2.81$, $p=.072$).

Congruency effects

There were significant main effects of congruency in terms of reaction times ($F_{1,71}=8.71$, $p=.004$), and accuracy rates ($F_{1,71}=8.00$, $p=.006$). These congruency effects were larger for motor switch trials than motor repeat trials (RT: $F_{1,71}=6.61$, $p=.012$; accuracy: $F_{1,71}=3.28$, $p=.074$) and for cognitive switch trials than for cognitive repeat trials (RT: $F_{1,71}=18.29$, $p<.001$; accuracy: $F_{1,71}=4.20$, $p=.044$), but there were no significant congruency \times group or subgroup interactions.

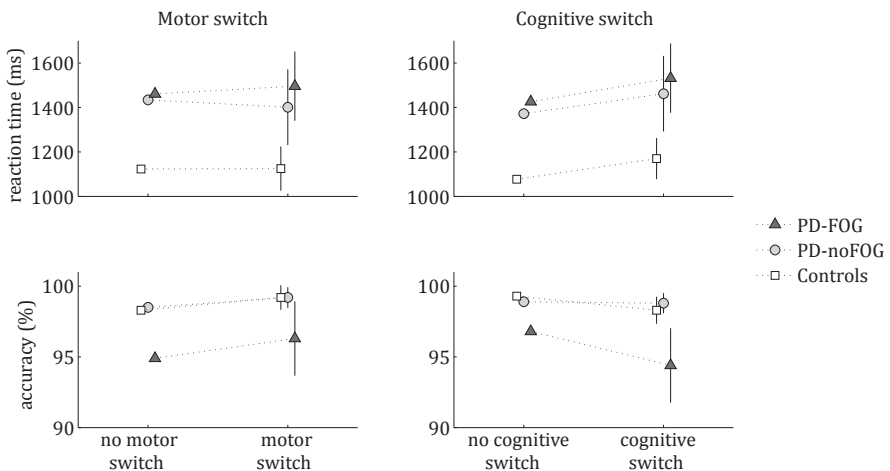


Figure 3. Performance on the motor and cognitive set switching task.

Estimated marginal means (error bars: SE of difference) for the reaction time without and with a motor **A.** and cognitive switch **B.**, and accuracy without and with a motor **C.** and cognitive switch **D.** for the three matched subgroups are presented.

Table 2: Uncorrected mean reaction times of (sub)groups for all trial types

	Reaction time (ms)			
	No switch	Motor switch	Cognitive switch	Motor and cognitive switch
Parkinson vs. healthy subjects				
HC	1064 (60)	1138 (62)	1253 (64)	1182 (59)
PD	1243 (50)	1344 (50)	1448 (55)	1355 (49)
Subgroups				
HC	1349 (126)	1395 (108)	1518 (129)	1407 (116)
PD-noFOG	1344 (97)	1507 (115)	1578 (120)	1486 (107)
PD-FOG	1042 (76)	1112 (72)	1204 (70)	1137 (65)

Uncorrected mean (SEM) reaction times for the four different trial types are presented for the PD patients (PD, n=51) and healthy controls (HC, n=22), and for the matched samples with PD patients with freezing of gait (PD-FOG, n=14), PD patients without freezing of gait (PD-noFOG, n=14), and healthy controls (n=14). Reaction times for congruent and incongruent trials are averaged.

Table 3: Uncorrected mean accuracy rates of (sub)groups for all trial types

	Accuracy (%)			
	No switch	Motor switch	Cognitive switch	Motor and cognitive switch
Parkinson vs. healthy subjects				
HC	99 (1)	98 (1)	96 (2)	99 (0)
PD	98 (1)	98 (1)	96 (1)	98 (1)
Subgroups				
HC	99 (1)	99 (0)	97 (2)	99 (0)
PD-noFOG	99 (1)	99 (1)	98 (1)	100 (0)
PD-FOG	97 (1)	96 (2)	93 (2)	96 (2)

Uncorrected mean (SEM) accuracy for the four different trial types are presented for the PD patients (PD, n=51) and healthy controls (HC, n=22), and for the matched samples with PD patients with freezing of gait (PD-FOG, n=14), PD patients without freezing of gait (PD-noFOG, n=14), and healthy controls (n=14). Accuracy rates for congruent and incongruent trials are averaged.

Simple reaction time

Patients with PD responded significantly more slowly on the SRT task than healthy controls ($F_{1,71}=10.77, p=.002$). There was a significant interaction effect of direction \times group ($F_{1,71}=6.58, p=.012$): PD patients had higher SRT's (+30 ms) on backward trials compared with forward trials ($t_{1,50}=-2.61, p=.012$), whereas

controls responded equally fast on these trial types ($t_{1,21}=1.45, p=.161$, Fig. 4).

PD-FOG, PD-noFOG and controls showed no significant differences in SRT ($F_{1,39}=3.06, p=.059$). However, the interaction effect of direction \times subgroup was again significant ($F_{1,39}=4.59, p=.016$). The PD-FOG group was 63 ms slower when stepping backwards compared with stepping forwards ($t_{1,13}=-3.36, p=.005$), whereas the PD-noFOG and controls had equally fast responses in both directions ($t_{1,13}=-0.101, p=.921$ and $t_{1,13}=1.64, p=.125$ respectively).

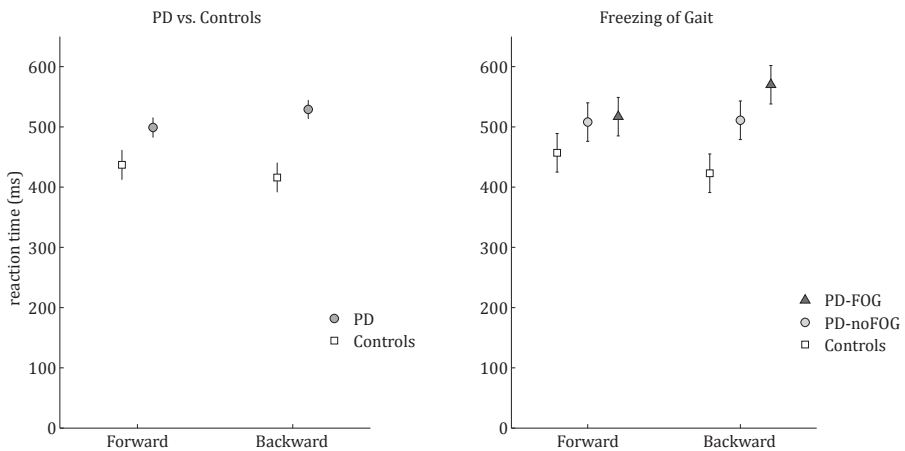


Figure 4. Performance on the simple reaction time task.

Mean values (error bars: SE) of the simple reaction time task for forward and backward stepping to a simple stimulus are presented for all PD patient and controls (left) and for the three matched subgroups (right).

Discussion

The aim of the present study was to assess the presence of motor and/or cognitive set switching deficits in PD patients with and without FOG. The results revealed a set switching impairment in patients with FOG that was restricted to switching between motor sets and did not extend to switching between cognitive sets. There was no generic PD switch impairment.

Our finding that PD patients with FOG, but not patients without freezing exhibit a set switching deficit extends previous findings by Naismith et al.¹⁷ who revealed problems with set switching on the Trail Making Test in freezers. The use of a more sophisticated experimental paradigm enabled us to go beyond this prior observation by comparing cognitive and motor types of set switching. Our data demonstrate that the switching deficit associated with FOG does not originate in cognitive inflexibility, but rather is due to a problem with switching

in the motor domain.

The observation that PD patients with FOG exhibit a set switching deficit during stepping supports the hypothesis that a change to an alternative motor set can induce FOG.³ In a previous study, PD patients walked in a straight line and were cued by a light to change walking direction.²⁹ Most freezes occurred when the light cue was presented during walking (in contrast to before walking), suggesting that it was not the advance planning that produced FOG, but rather the short-term set switch. Although we did not observe actual freezing episodes during task performance, our results generally concur with this conclusion.

The absence of a generic PD set switching impairment is in contrast with previous research, which has established both cognitive and motor switching deficits in PD.^{6-11,14-16,30,31} Multiple factors might account for this discrepancy. First, the set switching deficit in PD has been argued to depend on the specific demands of the task under study, with only certain forms of switching being sensitive to the early mild stages of the disease. In particular, certain types of cognitive set switching deficits are known to surface only in the more severe disease stages.³⁰ The PD patients in our study had mild to moderate disease severity ($H\&Y < 3$) relative to that in previous studies.^{9,14-16,30,31} Second, set switching is well established to be sensitive to treatment with dopaminergic medication.^{9,13,28} The patients in our study performed the assessment after withdrawal from all dopaminergic medication for at least 12 hours. Although such overnight withdrawal protocols are generally used to reach an “off” state in PD, it is well accepted that complete washout requires several days of abstinence.³² Hence, incomplete washout of dopaminergic medication might have reduced any differences between healthy subjects and patients. The factors of task demands, disease severity and dopaminergic medication might also interact. Thus the antiparkinsonian dopaminergic medication has been argued to be particularly beneficial for switching between well learned stimulus-response mappings.^{13,28,33} By contrast, problems with more abstract switch operations, such as cognitive set switching, might reflect non-dopaminergic processes outside the basal ganglia,³⁴ not yet affected in the early stages of the disease.

Given that stimulus switching and motor switching are associated with basal ganglia function, one would expect that the motor switch deficit would not be confined to the PD patients with FOG. Inflexibility in the motor domain has been demonstrated using different types of motor tasks.^{7,9,11,35,36} Our findings do not support this general motor inflexibility and leave us with the admittedly speculative question whether the motor switch impairments in previous studies were driven by patients with FOG.

Although the motor switch affected the stepping response in PD with FOG, this

impairment was smaller when the motor switch was accompanied by a cognitive switch. One might have expected that impairment in motor set switching would also be manifest in this latter condition. This finding is however less surprising given previous results showing that a more abstract cognitive switch can remediate a lower-order stimulus-motor switch impairment in patients with focal basal ganglia lesions.³⁷ Specifically, we have previously shown that a stimulus-switch impairment in patients with basal ganglia lesions disappeared when accompanied by a switch in abstract rules. We reasoned that perhaps the rule switch induced a bias to apply a switch operation in a relatively generic manner (see ³⁸). Thus, the cue to switch the rule may have biased the participants to also switch to the other stimulus pattern, a bias that in this case would lead to a correct response. A similar account might hold for the current finding.

In this study we chose stepping instead of key pressing or verbal responses, as this is more closely related to gait. The downside of this choice is that delays may be attributed to (feelings of) postural instability and gait disability (PIGD). In a supplementary analysis, we tested whether differences in PIGD between freezer groups confounded our findings (see Supplementary material). Alternatively, slow stepping reaction times can reflect general slowness of central processing. However, the groups had comparable SRT's. This strengthens our finding that the slower response in case of a motor switch in PD with FOG reflects a set switching deficit rather than postural instability or general slowness.

Our research sample was limited to mild to moderate PD patients without global cognitive impairments. However, executive dysfunction is reported even in the earliest stages of the disease.^{39,40} With further disease progression, additional cognitive functions become affected,⁴¹ possibly influencing gait and postural stability. This limits generalization of these findings to advanced disease stages. A second limitation was that our paradigm is particularly related to start hesitation. Whether set switching deficits also contribute to freezing episodes during other forms of FOG (i.e. turning) requires further investigation.

Our findings suggest that set switching deficits, commonly reported in tasks using verbal or tapping responses, extend to stepping and possibly contribute to the occurrence of freezing episodes. Future research should address the question whether and how a set switching deficit translates directly into freezing episodes. We hypothesize that set switching difficulty results in prolonged preparation of the step, disrupting the execution of the step, eventually leading to a freezing episode.

Supplementary material: Controlling PIGD

Methods:

Items 27-30 of the UPDRS-III (arising from chair, posture, gait, postural stability) were summed to calculate postural instability and gait disability (PIGD) scores of the PD patients. PIGD scores were compared between the PD-FOG and PD-noFOG group using an independent t-test.

We tested whether PIGD could explain differences in set switching effects on reaction times between PD-FOG and PD-noFOG. Hereto we added PIGD scores as a covariate to the general linear model with repeated measures (GLM-RM), with PD group as a between-subject factor with two levels (PD-FOG vs. PD-noFOG) and within-subjects factors cognitive switch (2 levels), motor switch (2 levels) and congruency (2 levels).

Results:

The PD-FOG group (4.1 ± 2.3) had significantly higher PIGD scores than the PD-noFOG group (2.4 ± 1.2 ; $t_{1,26} = -2.36$, $p = .026$).

The GLM-RM with PIGD as covariate yielded comparable results to the models without PIGD as covariate; We observed a significant motor switch \times PD group effect ($F_{1,25} = 4.52$, $p = .044$, Supplementary Table), indicating a motor switch deficit for the PD-FOG group. In contrast, there was no significant cognitive switch \times PD group interaction ($F_{1,25} = 0.12$, $p = .734$). There was a significant main effect of cognitive switch ($F_{1,25} = 9.27$, $p = .005$), but no main effect of motor switch ($F_{1,25} = .01$, $p = .914$). Reaction times did not differ between PD-FOG and PD-noFOG ($F_{1,25} = .01$, $p = .950$).

Supplementary Table. Switch effects on reaction times of PD-FOG and PD-noFOG controlling PIGD

	Cognitive switch				Motor switch			
	No switch	Switch	F	p	No switch	Switch	F	p
PD-noFOG	1408 \pm 117	1501 \pm 124	0.12	.734	1470 \pm 124	1439 \pm 117	4.52	.044
PD-FOG	1390 \pm 117	1494 \pm 124			1425 \pm 124	1459 \pm 117		

Estimated marginal means \pm SE of reaction times derived from the GLM-RM with covariate PIGD are presented for the two PD groups. F- and p-values represent the cognitive and motor switch \times PD group interactions.

References

1. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord.* 2004;19(8):871-84.
2. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA. Predictors of future falls in Parkinson disease. *Neurology.* Jul 13 2010;75(2):116-24.
3. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* Aug 2011;10(8):734-44.
4. Latt MD, Lord SR, Morris JGL, Fung VSC. Clinical and Physiological Assessments for Elucidating Falls Risk in Parkinson's Disease. *Mov Disord.* Jul 15 2009;24(9):1280-9.
5. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur J Neurol.* Jul 2003;10(4):391-8.
6. Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. *Brain.* Apr 1987;110 (Pt 2):361-79.
7. Chong RK, Horak FB, Woollacott MH. Parkinson's disease impairs the ability to change set quickly. *J Neurol Sci.* 2000;175(1):57-70.
8. Cools AR, van den Bercken JH, Horstink MW, van Spaendonck KP, Berger HJ. Cognitive and motor shifting aptitude disorder in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* May 1984;47(5):443-53.
9. Hayes AE, Davidson MC, Keele SW, Rafal RD. Toward a functional analysis of the basal ganglia. *J Cogn Neurosci.* 1998;10(2):178-98.
10. Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. *J Neurol Sci.* 1992;111(1):46-58.
11. Robertson C, Flowers KA. Motor set in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* Jul 1990;53(7):583-92.
12. Bowen FP, Kamienny RS, Burns MM, Yahr M. Parkinsonism: effects of levodopa treatment on concept formation. *Neurology.* Aug 1975;25(8):701-4.
13. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex.* Dec 2001;11(12):1136-43.
14. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain.* Dec 2001;124(Pt 12):2503-12.
15. Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia.* 1989;27(11-12):1329-43.
16. Owen AM, James M, Leigh PN, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain.* 1992;115 (Pt 6):1727-51.
17. Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. *Mov Disord.* Jun 15 2010;25(8):1000-4.
18. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg*

- Psychiatry*. Mar 1992;55(3):181-4.
19. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967;17(5):427-42.
 20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-98.
 21. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders : DSM-IV-TR*. 4th text revision ed. Washington, DC: American Psychiatric Association; 2000.
 22. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. Nov 15 2008;23(15):2129-70.
 23. Nieuwboer A, Rochester L, Herman T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture*. Nov 2009;30(4):459-63.
 24. Schmand B, Bakker D, Saan R, Louman J. [The Dutch Reading Test for Adults: a measure of premorbid intelligence level]. *Tijdschr Gerontol Geriatr*. Feb 1991;22(1):15-9.
 25. Brainard DH. The psychophysics toolbox. *Spat Vis*. 1997;10(4):433-6.
 26. Pelli DG. The VideoToolbox software for visual psychophysics: Transforming numbers into movies. *Spat Vis*. 1997;10(4):437-42.
 27. Kleiner M, Brainard D, Pelli D. What's new in Psychtoolbox-3? *Perception*. 2007;36:14.
 28. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*. 2003;41(11):1431-41.
 29. Knobl P, Kielstra L, Almeida Q. The relationship between motor planning and freezing of gait in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Jan 2012;83(1):98-101.
 30. Kehagia AA, Cools R, Barker RA, Robbins TW. Switching between abstract rules reflects disease severity but not dopaminergic status in Parkinson's disease. *Neuropsychologia*. Mar 2009;47(4):1117-27.
 31. Owen AM, Beksinska M, James M, et al. Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia*. 1993;31(7):627-44.
 32. Hauser RA, Koller WC, Hubble JP, Malapira T, Busenbark K, Olanow CW. Time course of loss of clinical benefit following withdrawal of levodopa/carbidopa and bromocriptine in early Parkinson's disease. *Mov Disord*. May 2000;15(3):485-9.
 33. Dang LC, Donde A, Madison C, O'Neil JP, Jagust WJ. Striatal dopamine influences the default mode network to affect shifting between object features. *J Cogn Neurosci*. 2012;24(9):1960-70.
 34. Kehagia AA, Murray GK, Robbins TW. Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. *Curr Opin Neurobiol*. Apr 2010;20(2):199-204.
 35. Cameron IG, Watanabe M, Pari G, Munoz DP. Executive impairment in Parkinson's disease: response automaticity and task switching. *Neuropsychologia*. Jun 2010;48(7):1948-57.
 36. Helmich RC, Aarts E, de Lange FP, Bloem BR, Toni I. Increased dependence of action

- selection on recent motor history in Parkinson's disease. *J Neurosci.* 2009;29(19):6105-13.
37. Cools R, Ivry RB, D'Esposito M. The human striatum is necessary for responding to changes in stimulus relevance. *J Cogn Neurosci.* Dec 2006;18(12):1973-83.
38. De Jong R, Liang CC, Lauber E. Conditional and unconditional automaticity: a dual-process model of effects of spatial stimulus-response correspondence. *J Exp Psychol Hum Percept Perform.* Aug 1994;20(4):731-50.
39. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology.* 2005;65(8):1239-45.
40. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. *Brain Pathol.* 2010;20(3):633-9.
41. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord.* 2008;23(6):837-44.

Chapter 8

Postural inflexibility in PD: Does it affect compensatory stepping?

Katrijn Smulders, Rianne Esselink, Bert de Swart, Alexander Geurts,
Bastiaan Bloem

Gait & Posture 2014;39(2):700-6

Abstract

Background: Parkinson's disease (PD) impairs the ability to shape postural responses to contextual factors. It is unknown whether such inflexibility pertains to compensatory steps to overcome balance perturbations.

Methods: Participants were instructed to recover balance in response to a platform translation. A step was necessary to recover balance when the translation was large, whereas a feet-in-place (FiP) response was sufficient when the translation was small (i.e. no step). We compared step trials that required a switch away from the current postural set (switch trials: step trials that were preceded by FiP trials) with non-switch trials (i.e. step trials were preceded by identical step trials). 51 PD patients (59 ± 7 yrs) were compared with 22 healthy controls (60 ± 6 yrs). In a second analysis, we compared a subgroup of 14 freezers (PD-FOG) with a subgroup of 14 non-freezers (PD-noFOG; matched for age, gender and disease severity).

Results: Compared to non-switch trials, switch trials resulted in poorer step execution and more steps needed to recover balance. These switching effects were similar in PD patients and controls, and in PD-FOG and PD-noFOG patients. Overall, PD patients demonstrated poorer stepping performance than controls. PD-FOG had a worse performance than PD-noFOG. Moreover, PD patients, and particularly PD-FOG patients, were less able to improve step performance with repetitive step trials, in contrast to controls.

Conclusion: There was no PD-related deficit to switch to an alternative response strategy, neither in patients with FOG nor in patients without FOG. Difficulty to adapt the step trial-by-trial might have contributed to the absence of switch deficits in PD.

Introduction

Parkinson's disease (PD) impairs the ability to successfully overcome postural perturbations, resulting in frequent falls.¹ The underlying mechanism of this incapacitating motor symptom remains poorly understood. Potentially, an impaired ability to adjust the postural response to the context of a task negatively affects stability.²⁻⁶ To appropriately respond to contextual factors, one should be able to flexibly switch between 'sets', thereby priming the nervous system to achieve the intended goal. In the current study we investigated whether this switching impairment contributes to the defective stepping responses in PD to overcome a postural perturbation.

Effects of 'set' have been assessed by exposing subjects to randomly sized perturbations and contrasting their performance with responses to blocks of identical perturbations,⁷⁻⁹ or to instruct the participants to respond with a certain strategy, for instance stepping,⁹ "resisting" or "giving".^{2,10} These manipulations generally result in modulation of the magnitude of the early, automatic postural response that helps stabilize the body. PD impairs this flexible adaptation driven by contextual factors.²⁻⁶ Previous research, however, was restricted to changes within one type of postural strategy set, in which the centre of mass (COM) is controlled without changing the base of support (feet-in-place strategy). With more challenging perturbations, balance is usually recovered by changing (enlarging) the base of support, i.e. by grasping for support or taking a compensatory step.¹¹

A very characteristic feature of postural instability in PD patients is their difficulty in taking compensatory steps in response to balance perturbations, particularly in the backward direction.^{3,12} We aimed to investigate whether inflexibility to changing *between* postural response sets (i.e. from feet-in-place to change-in-support strategy) may contribute to their impairments in compensatory stepping. For this purpose, we compared compensatory stepping responses to backward balance perturbations preceded by a series of feet-in-place (FiP) responses (inducing a switch away from the current postural set) with stepping responses preceded by a sequence of stepping responses (i.e. non-switch).

A second aim was to investigate whether postural inflexibility may be related to freezing of gait (FOG). FOG episodes often occur when changes in the intention of movement are required, such as turning and gait initiation.¹³ Interestingly, PD patients with FOG demonstrate more severe set switching impairments in the cognitive domain compared to non-freezing PD patients.¹⁴ We therefore conducted a matched subgroup analysis to compare the effects of changes in postural set between PD patients with and without FOG.

Subjects and methods

Subjects

Fifty-one patients with Parkinson's disease (69% men, age 59 ± 7) were recruited from the outpatient clinic of the Radboud University Nijmegen Medical Centre and were screened by a neurologist trained in movement disorders. Inclusion criteria were Parkinson's disease (UK Brain Bank Criteria),¹⁵ Hoehn & Yahr (H&Y) stage < 3 ,¹⁶ and aged between 18 and 70 years. Exclusion criteria were Mini Mental State Examination < 24 ,¹⁷ clinically relevant depression or anxiety disorders according to DSM-IV,¹⁸ any visual or vestibular impairment or physical inability to perform the assessments. Twenty-two healthy control subjects were recruited from the community (64% men, age 60 ± 6 yrs). All subjects gave their written informed consent before the assessments. Patients with PD performed the assessments after overnight withdrawal of all dopaminergic medication for at least 12 hours (OFF state). PD patients and healthy subjects did not significantly differ with regard to age ($p=0.791$) or gender ($p=0.677$). The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen).

Clinical assessment

Severity of defective motor function was assessed in all patients with PD using the Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III (MDS UPDRS-III)¹⁹ and disease stage was scored using H&Y stages. The New Freezing of Gait Questionnaire (NFOG-Q)²⁰ was filled out to identify patients with freezing of gait in daily life (scores > 0).

To compare PD patients with freezing of gait (PD-FOG, $n=14$) to those without freezing of gait (PD-noFOG), for each PD patients with freezing of gait we identified the best matching subject from the PD-noFOG group in terms of gender, age, and MDS UPDRS-III score. The matched samples did not differ significantly on any of the clinical and demographical parameters (Table 1).

Equipment

A moveable platform (120 x 180 cm, BAAT, The Netherlands, Figure 1A) was used to induce backward balance perturbations, using translations along the anterior-posterior axis. The direction of the balance perturbation was opposite to the direction of the platform translation, i.e. forward translation induced backward perturbation. From here, we will refer to the direction of the balance perturbation. All perturbations involved 300 ms of acceleration, 500 ms of constant velocity, and 300 ms of deceleration. Participants wore a safety harness attached to the ceiling to prevent them from falling.

Kinetic data was recorded from two force plates (60 x 180 cm, AMTI Custom 6-axis composite force platform, USA; sample rate 1000 Hz) embedded in the moveable platform. The subjects stood barefooted with each foot on one force plate. An 8-camera motion analysis system (Vicon Motion Systems, UK) was used to collect kinematic data (sampled at 100 Hz). Reflective markers were placed at the legs and trunk according to the Vicon Plug-in-Gait model.²¹

Table 1: Demographic and clinical characteristics of the participants.

			Total sample		Matched subgroups			
			PD	Controls	P	PD-noFOG	PD-FOG	P
n			51	22		14	14	
Age			59 (7)	60 (6)	.791	60 (7)	58 (8)	.447
Gender (%M)			69%	64%	.677	64%	64%	.000
MMSE			29 (1)			29 (1)	29 (1)	.000
MDS UPDRS-III			30 (13)			36 (10)	38 (12)	.697
H&Y	1		1 (2%)			0	0	.246
	1.5		2 (4%)			0	0	
	2		36 (71%)			10 (71%)	7 (50%)	
	2.5		12 (24%)			4 (29%)	7 (50%)	

Mean (sd) values are presented for all PD patients and healthy controls, and for the matched subgroups (PD-noFOG: PD patients without freezing of gait; PD-FOG: PD patients with freezing of gait). P-values represent the level of significance for the comparison between groups. MMSE: Mini-Mental State Examination; MDS UPDRS-III: Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (motor examination part); H&Y: Hoehn and Yahr stage

Procedure

We used backward perturbations to induce steps, because postural instability in PD patients is more pronounced in the backward than in the forward direction.^{3,12} Low acceleration trials at 0.25 m.s^{-2} resulted in a small perturbation that could be overcome without making a step (FiP response), and high acceleration trials at 1.25 m.s^{-2} resulted in larger perturbations that required a step to maintain balance (step response). Intertrial intervals varied randomly between 10 and 15 s. Hence, the start of the perturbation was unpredictable. The instruction was to respond naturally.

The assessment started with a step-evoking perturbation that was not announced, and thus completely unexpected, to abolish the a 'first trial effect' of the very first trial.^{22,23} Following this, eight successive step trials were presented, thereby requiring no change from postural set (non-switch condition; Figure 1C). Participants were informed that the perturbations would have a large amplitude,

requiring them to take a step in response to these perturbations. Immediately following this series, 47 trials were presented of which 7 were step trials and 40 were FiP trials. Participants did not know when in the series the step trials were planned. Four of the 7 step trials were preceded by a series of 8 FiP trials, hence requiring a switch away from a FiP set to a step response (switch condition). The other 3 step trials were used as catch trials, preceded by 1, 3 or 4 FiP trials, to ensure that participants could not predict the next step trial by counting FiP trials.

During the experimental tasks, no falls or freezing of gait episodes occurred. Moreover, the participants were always able to recover from the perturbation without support of the safety harness or grabbing the rails that surrounded the platform.

Data analysis

Ground reaction forces were low-pass filtered offline (2nd order 20 Hz low-pass butterworth). Step onset was defined as the time between start of the platform movement and the instant that the vertical ground reaction force was <10 N. The end of the step was determined as the first instant after step onset when vertical ground reaction force exceeded 10 N. Step onsets and end of steps were determined using a Matlab algorithm, followed by visual inspection.

Marker position data was filtered offline (2nd order 10 Hz low-pass butterworth). Platform movement was subtracted from the marker position data. Step length was calculated as the anterior-posterior change in toe marker position (2nd metatarsal) of the stepping leg between onset and end of the step. We determined the body configuration at the end of the step in terms of trunk and leg angle in the sagittal plane (Figure 1B).^{24,25} Trunk angle was calculated as the angle between the vertical and a line connecting the upper trunk (midpoint between markers at C7 and clavícula) and the pelvis (midpoint between markers at left and right anterior inferior and superior iliac spinae). A larger trunk angle indicated a more forward tilted trunk. The leg angle was defined as the angle between the vertical and a line connecting the pelvis and the toe marker of the stepping leg. A larger leg angle indicated a more backward-positioned foot with regard to the pelvis. This body configuration has shown to be highly predictive of balance recovery success.²⁵ In two PD patients, trunk angles could not be calculated due to reduced visibility of the trunk markers.

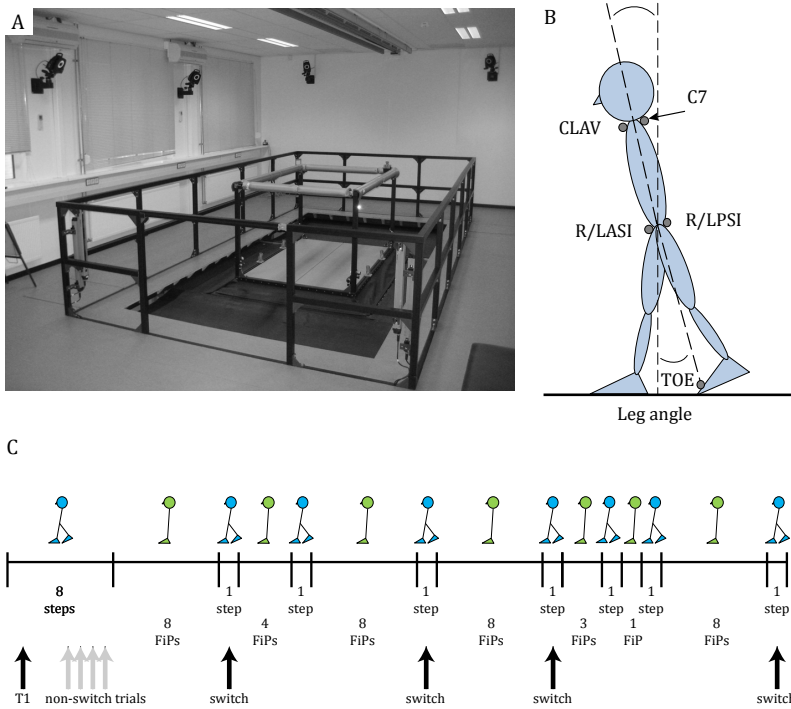


Figure 1: **A.** The moveable platform. **B.** Definitions of leg and trunk inclination angles. Trunk angle was calculated as the angle between the vertical and a line connecting the upper trunk and the pelvis. The upper trunk was determined as the midpoint between markers C7 and clavicle (CLAV). The pelvis was defined as the midpoint between the left and right anterior inferior (R/L ASI) and superior iliac spinae (R/L PSI). The leg angle was defined as the angle between the vertical and a line connecting the pelvis and the toe marker of the stepping leg (TOE). Depicted are positive inclination angles associated with a more favorable body configuration to recover balance. **C.** The series of 55 perturbations consisting of 8 consecutive step trials, followed by 7 series of perturbations that varied in the number of feet-in-place (FiP) trials that preceded the step trial. Four series of 8 FiP – 1 step trial were interspersed with three series consisting of 4, 3, or 1 FiP trials followed by a step trial ('catch' trial). The four last trials from the series of only step trials (non-switch condition; white arrows) were compared with the four step trials that were each preceded by 8 FiP trials (switch condition; dark grey arrows). Motor adaptation within the first series of step trials was estimated by comparing the very first step trial (T1; black arrow) with non-switch trials.

Statistical analysis

The average outcomes over the final four trials of the first step series (non-switch condition) were compared with those of the four step trials that were preceded by a series of FiP trials (switch condition). A 2 x 2 general linear model with

repeated measures (GLM-RM) with within-subjects factor 'postural set' (non-switch vs. switch) and between-subjects factor 'PD group' (PD patients vs. healthy subjects) was constructed. A similar model was used to compare PD subgroups (PD-FOG vs. PD-noFOG). Significance of all effects was accepted at $p < .05$.

To assess whether participants acquired a 'stepping' postural set, the first trial (T1) of the series of 8 step trials was compared with the last four step trials of this series (non-switch) using paired t-tests for each (sub)group separately. Significance of these tests was accepted at $p < .01$ to adjust for multiple comparisons.

Results

PD patients vs. healthy controls (Figure 2)

Across postural set conditions, PD patients did not differ from healthy subjects with regard to step onset ($F_{1,71}=0.42, p=.518$), or step length ($F_{1,71}=2.52, p=.117$). Yet, PD patients had 3° smaller leg angles ($F_{1,71}=7.84, p=.007$) and 4.2° larger trunk angles ($F_{1,69}=7.04, p=.010$) than healthy subjects. Furthermore, PD patients needed significantly more steps than healthy controls to overcome the perturbation (respectively 1.4 ± 0.1 vs. 1.1 ± 0.1 steps; $F_{1,71}=6.10, p=.016$).

Compared with non-switch trials, the leg angle ($-0.7^\circ, F_{1,71}=4.02, p=.049$) and trunk angle ($-1.2^\circ, F_{1,69}=14.43, p<0.001$) were reduced in switch trials, and participants needed more steps to regain stability (1.2 ± 0.6 vs. 1.3 ± 0.7 steps; $F_{1,71}=6.89, p=.011$). Step onset ($F_{1,71}=0.86, p=.356$) and step length were not affected by postural set ($F_{1,71}=0.01, p=.929$). Importantly, the effect of postural set was comparable between PD patients and healthy subjects, as evidenced by the absence of significant postural set-by-group interaction effects (all p -values $> .05$).

Freezers vs. non-freezers (Figure 3)

PD patients with freezing of gait responded to the perturbation with significantly smaller step lengths (-4.8 cm, $F_{1,26}=4.795, p=.038$) and leg angles ($-4.4^\circ, F_{1,26}=9.05, p=.006$) compared with non-freezers. Step onset, trunk angle and number of steps were not significantly different between PD-FOG and PD-noFOG (all p -values $> .05$).

Trials requiring a switch resulted in deteriorated leg ($F_{1,26}=5.72, p=.024$) and trunk angles ($F_{1,25}=10.25, p=.004$) when compared with trials without a switch. No postural set effects were observed on step onset, step length, or number of steps (all p -values $> .05$). Again, postural set effects did not differ between PD-FOG and PD-noFOG (no significant postural set-by-PD subgroup effects, all p -values $> .10$).

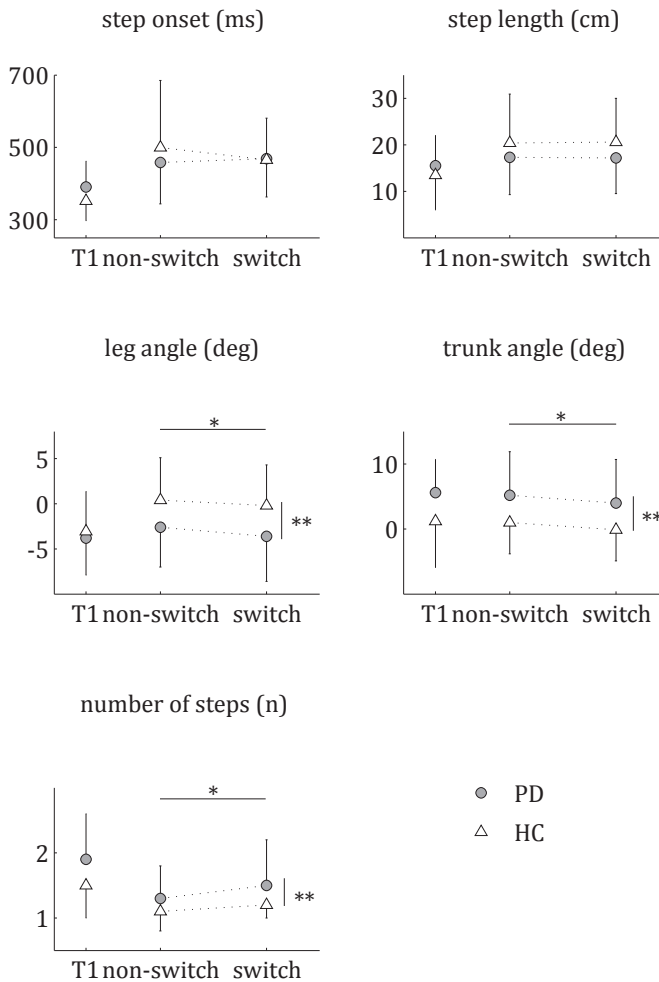


Figure 2. Mean and standard deviations for trials with and without a switch, and for the first step trial of the series of step trials (T1) are presented for PD patients (PD; grey circles) and healthy subjects (HC; white triangles).

* $p < .05$ for main effect of postural set, ** $p < .05$ for main group effect

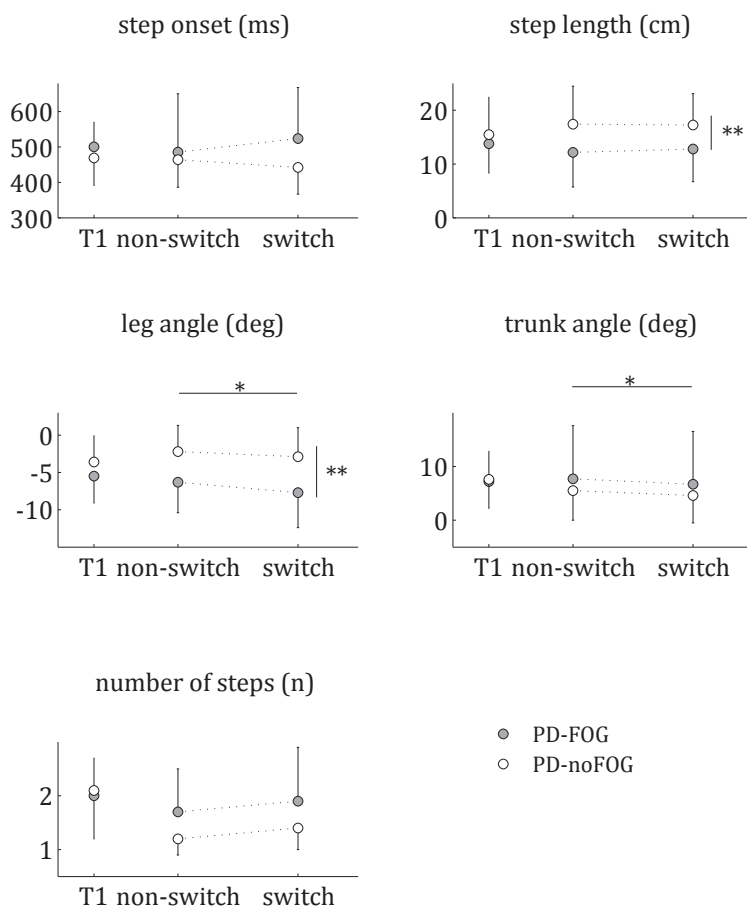


Figure 3. Mean and standard deviations for trials with and without a switch, and for the first step trial of the series of step trials (T1) are presented for PD patients with freezing of gait (PD-FOG; grey circles) and without freezing of gait (PD-noFOG; white circles).

* $p < .05$ for main effect of postural set, ** $p < .05$ for main PD subgroup effect

Postural set acquisition (Table 2)

Healthy subjects improved their performance from T1 to the last four step trials on step length, leg angle and number of steps (all p -values $\leq .005$), but had later step onsets ($p < .001$). PD patients only modulated step onset (later step onset, $p < .001$) and number of steps (fewer steps, $p < .001$). These effects in PD patients were only present in the PD-noFOG group. PD-FOG did not modulate any of the step variables (all p -values $> .100$).

Table 2: Adaptation of the step parameters over the course of 8 successive step trials

	HC	PD	PD-noFOG	PD-FOG
Step onset	<.001	<.001	.107	.002
Step length	.005	.114	.435	.432
Leg angle	.005	.036	.965	.372
Trunk angle	.034	.026	.779	<.001
Number of steps	<.001	<.001	.149	<.001

P-values in bold represent significant differences between the first trials of the step series (T1) and the last four trials (T5-8) of this series, indicating motor adaptation. Significance was accepted at $p < .01$.

Discussion

We investigated whether step characteristics are affected by the need to switch away from a postural response set, and whether patients with PD with and without freezing are impaired in this kind of switching. Our results show that the body configuration at the end of the step was less beneficial when participants needed to switch from a feet-in-place set to a step response and that more steps were needed to recover balance. However, these switching effects were similar for PD patients and healthy subjects, as well as for PD patients with and without freezing of gait.

The steps to recover balance were induced by identical perturbation magnitudes, but the critical difference between our two postural set conditions was that the steps were either preceded by a sequence of perturbations also requiring steps, or by a sequence of low-magnitude perturbations to which people responded with a feet-in-place strategy. Hence, the postural switch effects could not originate from differences in sensory input or differences in destabilizing forces. Presumably, experience from prior trials biased the participants to either a step or FiP response. For all groups, the need to switch away from this postural set resulted in less efficient stepping, as evidenced by less beneficial body configurations (i.e. smaller leg and trunk angles) at the end of the step and the need to take more steps to recover balance.

Crucially, the effect of a switch of postural set did not differ between healthy subjects and PD patients, which was true both for freezers and non-freezers. Hence, we found no evidence of a PD-related inflexibility in switching from one postural response strategy (i.e. feet-in-place) to another (i.e. stepping). This finding is in contrast with previous research reporting detrimental effects of set changes in PD patients on the amplitudes of automated postural responses.²⁻⁶ Thus, the question arises whether this scaling deficit previously observed in the

earliest response phases extends to postural responses that require stepping. Our results suggest that destabilizing effects of set switching in the early response stage are so minor that they do not substantially impact the overall performance of a recovery step.

It must be mentioned, however, that the PD patients exhibited reduced adaptation in step parameters over the course of the eight successive step trials. Providing subjects with a series of identical perturbations enables them to learn from the stimulus and the outcome of the accompanying response.²³ The PD patients, but particularly the PD patients with freezing of gait, had much more difficulty to improve their step from trial to trial. Hence, the absence of a PD-related disproportionate effect of postural set on step performance may also be (partly) due to the reduced motor adaptation with repeated stepping. This rigidity concurs with previous perturbation studies reporting an inability to adapt the amplitudes of automated postural responses to contextual factors (instruction or magnitude predictability) in PD.²⁻⁶

At the end of the step PD patients were mechanically more unstable than their healthy peers, as evidenced by their smaller stepping leg angles and the larger number of steps needed to recover balance. PD patients with freezing of gait performed even worse compared with non-freezers. Patients with freezing of gait also demonstrated decreased step lengths, which presumably contributed to their reduced leg angles. In contrast, the PD patients had a slightly more forward tilted trunk than controls, which is biomechanically beneficial to overcome backward perturbations.^{24,25} This may be related to the 'stooped' posture in PD, which has been postulated as a mechanism to compensate for postural instability in the backward direction.²⁶ However, the possible beneficial forward tilt of the trunk was likely outweighed by their poorer leg angles, as evidenced by the larger number of steps needed. This concurs with the previous observation that an increase of almost 3° in trunk angle was needed to compensate for a 1° decrease in leg angle.²⁵

The reduced leg angle in PD patients reflects the hypometric nature of postural responses of PD patients that were previously reported in compensatory stepping²⁷ and self-initiated stepping.²⁸ Hypometric responses can be the consequence of underscaling of motor commands, resulting in insufficient joint torques.²⁹ This may lead to slowing of movement speed (bradykinesia). In our study, the attenuated stepping amplitude does not seem to be related to slowness of preparatory movements for step initiation, since the step onset was unaffected.

Our study results are limited to step kinematics, but EMG recordings from the muscles involved in balance recovery might further our understanding of postural set effects. Since the automatic postural response, step initiation and

execution are overlapping processes, it might be challenging, but insightful to tease out set effects in each phase of balance recovery. Additionally, recent work shows promising directions for the use of electroencephalography (EEG) to study cortical involvement in postural responses and postural set changes that are apparent before the onset of perturbation.^{6,30}

The patients in our study performed the tasks off dopaminergic medication. Although cognitive set switching has been reported to be sensitive to dopaminergic medication,³¹⁻³³ such an effect has not been found with regard to the ability to adapt postural responses to changes in contextual factors.^{2,4,8} However, given the key role of dopamine in learning,³⁴ it would be interesting to test how dopamine mediates the acquisition of postural sets.

In conclusion, the present study shows that the need to suddenly switch to an alternate postural response strategy results in a less efficient corrective step both in PD patients and in healthy subjects. Although PD patients, and particularly PD freezers, demonstrated poorer step responses to overcome an external perturbation than healthy subjects, a switch to a different postural response set did not further worsen their performance. We did, however, observe a reduced ability in PD freezers to adapt the step within a series of steps, which might reflect difficulty to acquire a postural set.

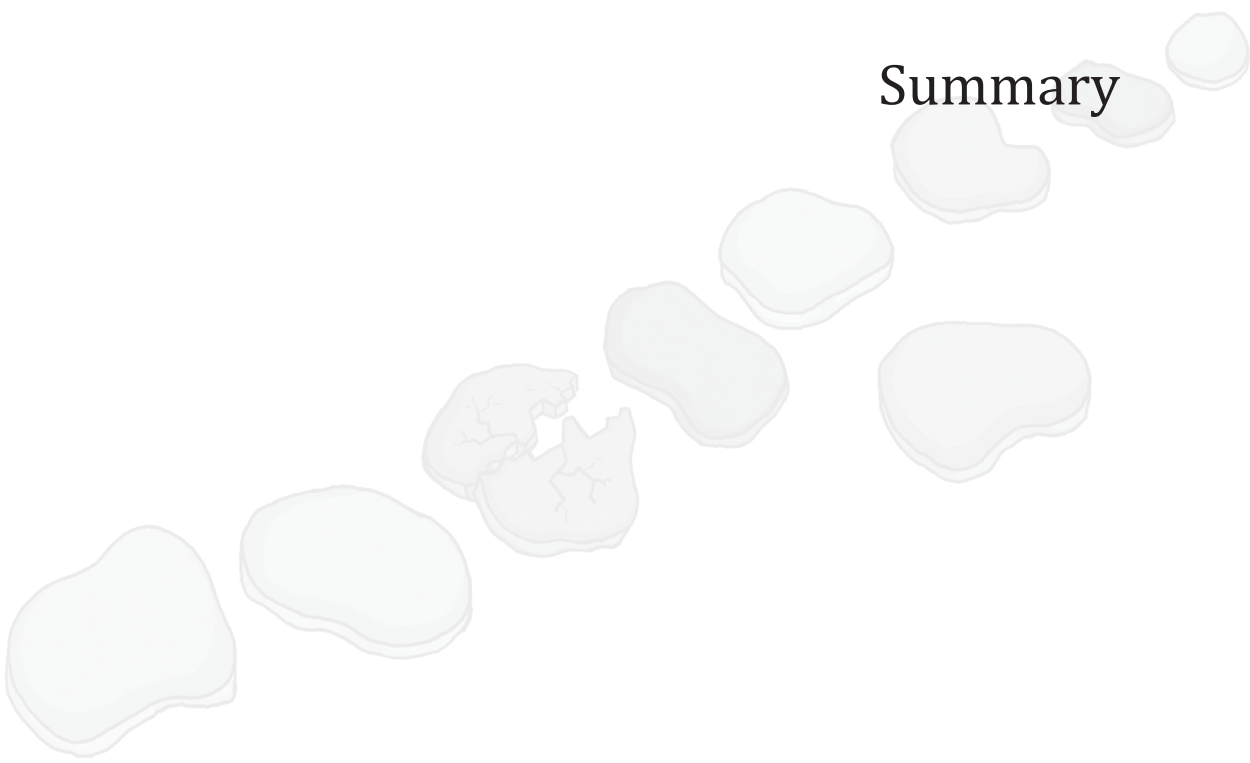
References

1. Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. *J Neurol*. 2001;248(11):950-8.
2. Chong RK, Horak FB, Woollacott MH. Parkinson's disease impairs the ability to change set quickly. *J Neurol Sci*. 2000;175(1):57-70.
3. Dimitrova D, Horak FB, Nutt JG. Postural muscle responses to multidirectional translations in patients with Parkinson's disease. *J Neurophysiol*. Jan 2004;91(1):489-501.
4. Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. *J Neurol Sci*. 1992;111(1):46-58.
5. Schieppati M, Nardone A. Free and supported stance in Parkinson's disease. The effect of posture and 'postural set' on leg muscle responses to perturbation, and its relation to the severity of the disease. *Brain*. Jun 1991;114 (Pt 3):1227-44.
6. Smith BA, Jacobs JV, Horak FB. Effects of magnitude and magnitude predictability of postural perturbations on preparatory cortical activity in older adults with and without Parkinson's disease. *Exp Brain Res*. Oct 2012;222(4):455-70.
7. Beckley DJ, Bloem BR, Remler MP, Roos RA, van Dijk JG. Long latency postural responses are functionally modified by cognitive set. *Electroencephalogr Clin Neurophysiol*. 1991;81(5):353-8.
8. Burleigh-Jacobs A, Horak FB, Nutt JG, Obeso JA. Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers. *Mov Disord*. Mar 1997;12(2):206-15.
9. McIlroy WE, Maki BE. Changes in early 'automatic' postural responses associated with the prior-planning and execution of a compensatory step. *Brain Res*. Dec 24 1993;631(2):203-11.
10. Bloem BR, Beckley DJ, Remler MP, Roos RA, van Dijk JG. Postural reflexes in Parkinson's disease during 'resist' and 'yield' tasks. *J Neurol Sci*. 1995;129(2):109-19.
11. Maki BE, McIlroy WE. The role of limb movements in maintaining upright stance: the "change-in-support" strategy. *Phys Ther*. May 1997;77(5):488-507.
12. Carpenter MG, Allum JH, Honegger F, Adkin AL, Bloem BR. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Sep 2004;75(9):1245-54.
13. Snijders AH, Haaxma CA, Hagen YJ, Munneke M, Bloem BR. Freezer or non-freezer: clinical assessment of freezing of gait. *Parkinsonism Relat Disord*. Feb 2012;18(2):149-54.
14. Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. *Mov Disord*. Jun 15 2010;25(8):1000-4.
15. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. Mar 1992;55(3):181-4.
16. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. 1967;17(5):427-42.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-98.

18. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders : DSM-IV-TR*. 4th text revision ed. Washington, DC: American Psychiatric Association; 2000.
19. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. Nov 15 2008;23(15):2129-70.
20. Nieuwboer A, Rochester L, Herman T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture*. Nov 2009;30(4):459-63.
21. Davis III RB, Ōunpuu S, Tyburski D, Gage JR. A gait analysis data collection and reduction technique. *Human Movement Science*. 1991;10(5):575-87.
22. Allum JH, Tang KS, Carpenter MG, Oude Nijhuis LB, Bloem BR. Review of first trial responses in balance control: influence of vestibular loss and Parkinson's disease. *Hum Mov Sci*. Apr 2011;30(2):279-95.
23. Nanhoe-Mahabier W, Allum JH, Overeem S, Borm GF, Oude Nijhuis LB, Bloem BR. First trial reactions and habituation rates over successive balance perturbations in Parkinson's disease. *Neuroscience*. Aug 16 2012;217:123-9.
24. Hsiao ET, Robinovitch SN. Elderly subjects' ability to recover balance with a single backward step associates with body configuration at step contact. *J Gerontol A Biol Sci Med Sci*. Jan 2001;56(1):M42-7.
25. Weerdesteyn V, Laing AC, Robinovitch SN. The body configuration at step contact critically determines the successfulness of balance recovery in response to large backward perturbations. *Gait Posture*. Mar 2012;35(3):462-6.
26. Dietz V, Zijlstra W, Assaiante C, Trippel M, Berger W. Balance control in Parkinson's disease. *Gait & Posture*. 1993;1(2):77-84.
27. Jacobs JV, Horak FB. Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease. *Neuroscience*. Aug 25 2006;141(2):999-1009.
28. Okada Y, Fukumoto T, Takatori K, Nagino K, Hiraoka K. Abnormalities of the first three steps of gait initiation in patients with Parkinson's disease with freezing of gait. *Parkinson's disease*. 2011;2011:202937.
29. Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. *Brain*. Nov 2001;124(Pt 11):2131-46.
30. Jacobs JV, Fujiwara K, Tomita H, Furune N, Kunita K, Horak FB. Changes in the activity of the cerebral cortex relate to postural response modification when warned of a perturbation. *Clin Neurophysiol*. Jun 2008;119(6):1431-42.
31. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*. Dec 2001;11(12):1136-43.
32. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*. Dec 2001;124(Pt 12):2503-12.
33. Hayes AE, Davidson MC, Keele SW, Rafal RD. Toward a functional analysis of the basal ganglia. *J Cogn Neurosci*. 1998;10(2):178-98.
34. Packard MG, Knowlton BJ. Learning and memory functions of the Basal Ganglia. *Annu Rev Neurosci*. 2002;25:563-93.

Chapter 9

Summary



Summary

In this thesis, I aimed to increase our understanding of the role of cognitive control on gait and balance, both in patients with stroke and patients with Parkinson's disease (PD). Stroke and PD are complementary with regard to disease onset and progress. A stroke occurs suddenly and has acute signs and symptoms. Stroke patients can improve considerably, particularly in the first months. In contrast, PD is a progressive and degenerative disease with gradual increase of symptoms and disease severity.

In the first part of my thesis, I assessed the automaticity of complex gait in community-dwelling patients with stroke and investigated whether this capacity can be improved by training. The gait task applied constituted of avoiding obstacles that were suddenly dropped in front of the affected foot while walking on the treadmill. In order to test the amount of attention needed to avoid the obstacles, the participants had to simultaneously respond to an auditory cognitive task (Stroop task). By comparing the performance on the gait and cognitive task in isolation and in combination, the dual task costs were assessed for both tasks (difference between single and dual task performance). In **chapter 2** I observed that the addition of the Stroop task resulted in a delay of the muscle responses, but that the success rate for obstacle avoidance was not affected. This dual task effect on the gait task was comparable for patients with stroke and healthy subjects. However, when analyzing their performance on the cognitive task, we observed differential dual task effects for the two groups. Patients with stroke showed a poorer performance on the cognitive task while they had to cross the obstacle than healthy controls. These findings suggest that the patients with stroke relied more heavily on cognitive resources to prevent stumbling when avoiding obstacles, thereby prioritizing the motor task. This strategy seems adequate considering that errors in obstacle crossing have much more severe consequences, such as tripping and falling, than deterioration in cognitive task performance.

In **chapter 3** we evaluated the effects of a gait adaptability training in patients with stroke using the same tasks as in chapter 2. Effects of the training on single task obstacle avoidance performance and the associated attentional demands were assessed. The intervention consisted of 10 training sessions using an instrumented treadmill on which visual cues were projected that were meant as a target for foot placement or served as obstacles that needed to be avoided. Pre- and post-training performance on the obstacle avoidance task (see chapter 2) was compared for both single and dual task conditions. Patients with stroke improved their obstacle avoidance success rates following training. This effect

was accompanied by better performance in dual task situations: the performance of the Stroop task improved by 5% while negotiating obstacles. The dual task costs did not differ between the pre- and post-test. Although this study lacked a control group, these results suggest that gait adaptability in the chronic phase of stroke is trainable, which was associated with a decrease in attentional demands.

The second part of this thesis focused on the cognitive control of gait and balance in patients with Parkinson's disease (PD). First, I tested the hypothesis that dual task deficits in PD patients might predispose them to falls (**chapter 4**). The idea behind this hypothesis is that PD patients do not efficiently allocate the available attentional resources to gait and stability when involved in multiple tasks. The presumed "posture second" strategy that PD patients would use could result in hazardous situations, and eventually in falls. We evaluated the dual task costs on gait parameters (unobstructed) and on the auditory Stroop task, comparing recurrent fallers with non-recurrent fallers. Contrary to our expectation, none of the dual task costs for the gait or Stroop task were different between recurrent and non-recurrent fallers. Because this finding does not rule out that PD fallers might have used a posture second strategy, I also analyzed the individual dual task costs on both tasks. However, this analysis showed that patients with multiple falls used similar strategies compared to those with no or one fall. Together, these findings led to the conclusion that dual task assessment is not a clinically valid method to predict fall risk in PD patients. Clinical measures (e.g. severity of motor symptoms) and single task walking parameters were better predictors than dual task costs.

Dual task paradigms allow us to estimate the amount of required cognitive resources, but this does not tell us which cognitive functions are involved in motor tasks. In the study presented in **chapter 5**, I specified cognitive control of motor tasks assessing four main components: working memory, set switching, inhibition and response generation. The aim of this study was to investigate the associations of these components with the Timed Up and Go (TUG) task and PIGD scores of the UPDRS III. Working memory and response generation were significantly, but weakly associated with the TUG test as well as with PIGD. When disease severity, age, and educational level were controlled for, only the association between TUG and response generation (semantic fluency) remained significant. None of the cognitive tests was an independent predictor of PIGD when disease severity, age, and educational level were controlled for. This study suggests that response generation and, to a lesser extent, working memory may be involved in a seemingly pure motor task.

In **chapter 6** the focus was on the inhibition component of cognitive control,

operationalized as trait impulsivity. In this chapter I hypothesized that impulsive behavior might predispose PD patients to falls. Indeed, recurrent fallers had higher impulsivity scores than non-fallers. This was particularly true for scores on attentional impulsivity. The second aim of the study was to test whether impulsivity modulates the relation between PIGD and fall risk, but the results did not provide evidence for that. This study provided the first evidence that impulsivity, in particular in the attentional domain, is associated with fall risk in PD.

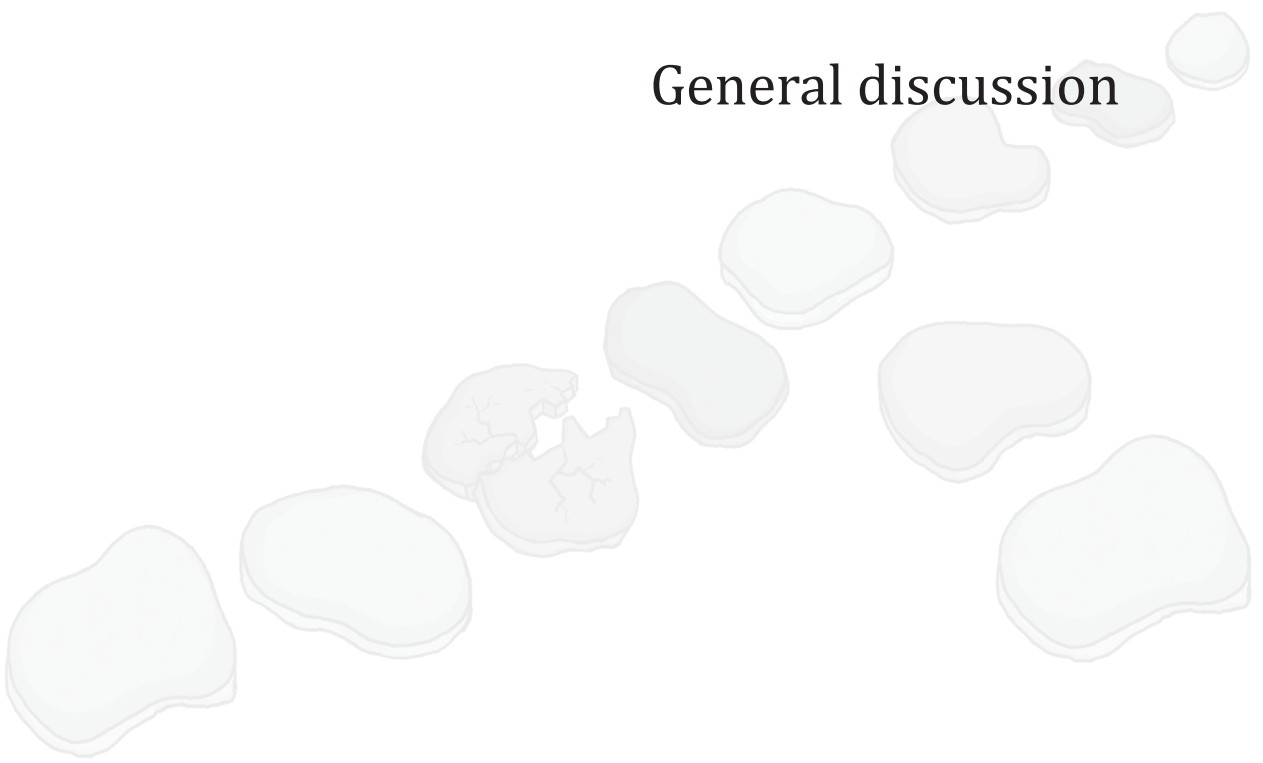
In **chapters 7 and 8**, I focused on the ability to switch between cognitive and motor sets in PD patients. PD affects the ability to flexibly switch between motor sequences or between cognitive rules. However, the contribution of these set switching deficits to the motor symptoms of PD patients, like bradykinesia and akinesia, is unclear. We hypothesized that set switching deficits might impair stepping, for example reflected by difficulties to initiate gait during freezing episodes. To test this hypothesis, I designed a paradigm integrating step initiation and set switching within one task that enabled direct comparison between switching in the motor and cognitive domains (**chapter 7**). The participants had to step forward or backward in response to a target presented on a computer monitor in front of them. A motor switch was defined as a change in stepping direction from one trial to the next. A cognitive switch was defined as a change in the relevant stimulus feature (shape or color). The results did not reveal a motor or cognitive set switching impairment in the PD patients when contrasted with healthy subjects. However, the PD patients with freezing of gait exhibited a significant motor set switching deficit, but not in the cognitive domain. These findings suggest that motor set switching deficits extend to stepping, and possibly contribute to the occurrence of freezing episodes in patients with PD.

To further explore the influence of set switching deficits on stepping responses in patients with PD, we investigated whether switching might impair stepping in response to a perturbation in **chapter 8**. Participants needed to respond to a platform translation. In case of a large translation, a step was required to recover balance. In case of a small translation, a feet-in-place (i.e. no step) response was sufficient. We applied two conditions: in the ‘no switch’ condition, the step was preceded by a series of other step-inducing perturbations. In this condition the perturbation was part of a series of identical perturbations and, therefore, the participant could use the experience of the preceding trials and set the postural system accordingly to optimize its response. In the ‘switch’ condition, the step was preceded by a series of perturbations inducing feet-in-place responses. Hence, the participant needed to shift away from a feet-in-place strategy and configure a stepping response. We found that in switch trials participants showed poorer

step characteristics in terms of leg and trunk angles and needed more steps to recover balance. Crucially, the effects of postural set were comparable for PD and healthy controls. Thus, we did not observe a switching impairment affecting compensatory stepping in PD, which was true for both patients with and without freezing of gait. An interesting observation was that freezers were less able to improve their stepping response within the series of steps. This suggests that this subgroup had more difficulty adapting their stepping responses by using the experience of previous, identical trials. This impaired motor adaptation might have confounded our findings with regard to the effects of switching.

Chapter 10

General discussion



General discussion

Paying attention to walking

As shown in the first part of this thesis, both patients with stroke and healthy controls need to pay attention to walking. When gait is impaired by a movement disorder, the amount of attention needed to maintain stability increases. Likewise, when gait capacity improves, the attentional demands decrease. The cognitive-motor dual task paradigm proved to be very sensitive to measure these effects in both directions.

Two theories have been postulated to explain this attention capacity interference.^{1,2} First, according to the capacity- or resource-sharing model, the performance in dual task situations depends on the motor skill, the cognitive skill, and the available attentional resources.² Through practice, a shift from reliance on cognitive (cortical) control mechanisms to reliance on faster, coordinated (subcortical) structures results in attenuated attentional demands. Consequently, more attentional reserve remains for the secondary task. In line with this notion, dual task deficits can also originate from reduced attentional resources (besides a poor skill level). Another theory to explain dual task performance is that attention capacity interference may improve as a result of enhanced efficiency within a structure or network that coordinates the use of attentional resources. However, there is still debate on the existence of such a structure.³⁻⁵

The dual task studies in this thesis were not designed to differentiate between these two theories. Still, the results might provide some leads to better understand the origin of the observed dual task interference and, thereby, to guide development of improved training programs. In **chapter 2** we observed that patients with stroke needed disproportionate attention *during* obstacle negotiation. This might have been caused by i) compromised gait adaptability, ii) an impaired ability to perform dual tasks, or iii) a generalized attention capacity deficit. Although the latter has previously been reported, even in well recovered patients after stroke,⁶ the absence of dual task interference while walking without obstacles suggests that the available capacity was at least to a certain extent intact. Moreover, in our dual task training study, patients with stroke were able to improve gait adaptability in single as well as in dual task conditions. This suggests that the dual task improvement was caused by enhanced gait adaptability rather than an improved ability to carry out dual tasks per se. Taken together, I would speculate that the dual task performance in community-dwelling patients with stroke in the studies of this thesis was predominantly influenced by their gait capacity.

In PD patients, it seems that dual task problems are driven by cognitive impairments. The ability to switch between tasks and inhibit the least relevant

task likely impacts on dual task performance. These cognitive processes can be affected in PD, already in early disease stages.⁷ Inadequate switching and inhibition might result in a suboptimal dual task behavior, such as a posture second strategy.⁸ However, the results of **chapter 4** do not support a general posture second strategy being present in most of the patients. Rather, the dual task costs of individual patients were distributed over both the cognitive and the motor tasks, which implies a variety of strategies. These results were recently confirmed in another study in which priority setting was manipulated directly.⁹ Still, it would be interesting to study whether and how switching and inhibition deficits compromise dual task performance in patients with PD.

How do these observations in patients with stroke and PD improve clinical practice? With regard to therapy, the Dutch guideline for physical therapy for PD states that dual tasks should be avoided because of the problems that most PD patients experience in such situations.¹⁰ However, given the fact that activities in daily life that are carried out in isolation are largely outnumbered by situations consisting of multiple tasks, the validity and in particular the practical feasibility of this recommendation can be questioned. Rather, one could consider an alternative possibility, such that dual task situations would be trained instead of avoided. We showed that a treadmill training aiming at a better ability to adapt ongoing gait to visual stimuli can improve complex gait capacity and decrease the associated attentional demands in patients with stroke. Currently, multiple (randomized controlled) trials are being conducted to test the efficacy and feasibility of dual task training programs after stroke as well as in patients with PD.¹¹⁻¹⁴ Particularly, studies that focus on training the capacity of these patients to perform dual tasks, in contrast to training the same tasks in isolation, will provide valuable information about the efficacy of dual task training programs in patients with neurological diseases (see [13] for an example).

Behavior in daily life versus experimental situations

A limitation of experimental testing in controlled situations is that what we assess reflects what people *can do* rather than what people *will do* in more natural environments. A laboratory setting allows to sensitively assess behavior in psychometric and physiological terms, thereby enabling to gain insights in specific pathologic processes. The downside is that the generalizability of results obtained in a laboratory setting to daily life situations can prove to be difficult. For example, a person with serious gait impairments can easily adjust his activity pattern to avoid balance-threatening situations, thereby reducing the risk of falls. Hence, behavioral strategies induce a gap between *can do* and *will do*.

In the dual task studies of this thesis I observed rather adequate strategies

(i.e. posture first) in both the patient with stroke and with PD. Still, we cannot rule out the possibility that participants adjusted their spontaneous behavior because they were instructed and monitored during the assessments. On the other hand, patients who are capable of using safe strategies will not necessarily use this capacity in daily life. These problems emphasize the need for measures that estimate actual behavior in daily life. In this thesis, I assessed a personal construct of behavior in chapter 6. I found an association between self-reported impulsive behavior and fall risk in PD. Interestingly, this finding was in line with a study assessing impulsivity using an experimental task, showing an association between impulse control and postural instability and gait disorders in PD.¹⁵ However, impulsivity is a complex concept and our study was only the second to investigate this type of behavioral influence on falls. Moreover, although the main findings of this study were in line with two previous reports using experimental tasks, there were also differences that might be attributable to differences in methodology: objective, experimental measurements such as a go/no go task, and the subjective, self-report measure that I used. The main finding that impulsivity scores were higher in recurrent fallers is nonetheless encouraging to further explore which aspects of impulsivity underlies this increased fall risk.

Gait and postural stability: switching perspectives

In the last chapters of this thesis I elaborated on the role of a set switching on stepping responses in PD. Set switching deficits are well established in PD patients, even the early stages of the disease,¹⁶⁻²² in both the cognitive and motor domain. The hypothesis was that set switching deficits might contribute to gait disability in PD.

Configuring or ‘setting’ the responsible systems in a way that one is ready to respond to a certain stimulus facilitates task performance. Task instruction, prior experience, and contextual factors can be used to adopt such a task set and prepare for the upcoming trial. In this way, a task set helps to stabilize the performance of an on-going task, and to protect it from distraction. The downside of high *stability* of a task is that it can obstruct the ability to *flexibly* switch to another task. This is illustrated by detrimental responses when one needs to switch to an alternate task set (higher reaction times and/or lower success rates).^{23,24}

In this thesis I used three types of switches (**chapters 7 en 8**). These switches can be best described in terms of stimulus-response mappings. In **chapter 7**, participants had to switch between different responses cued by different visual stimuli. In **chapter 8**, I studied the effects of switches in context while the stimuli and responses were identical in each condition. The findings in **chapter 7** suggest that a switching deficit in the motor domain might contribute to gait disability,

and more specifically to freezing of gait. Such a motor switch deficit was, however, not found in PD freezers in the **chapter 8**, where participants needed to take a step in response to a perturbation. Two factors may account for this discrepancy. First, the stepping responses in the two studies were different with regard to the nature of the stimulus and the association between the stimulus and the response. In **chapter 7**, participants had to step as a reaction to a visual stimulus, whereas the stimulus in **chapter 8** was a postural perturbation. The latter can be considered a much more urgent cue that is by nature strongly associated with the step response. This would imply that different neural pathways are involved in the two stepping tasks. Second, the findings in the perturbation study suggest that PD patients with freezing of gait had more difficulty to adapt and improve the step characteristics already from the first trial onward. This might indicate that the task set was less well established by the freezers which, consequently, may have confounded the switch costs that were observed.

Cognition and movement: separate entities?

In this thesis I investigated to what extent gait, stepping and postural stability are under cognitive control, and which specific cognitive functions might be involved. While discussing the results of the different studies, it became clear that the tasks and processes under investigation could not easily be separated into either 'motor' or 'cognitive' domains. This raises the question whether cognition and movement can be regarded as separate entities.

It is of course possible to think of examples of a 'pure' motor or cognitive task. A pure motor task should be independent of any cognitive control, e.g. exemplified by a headless, running chicken. Similarly, a pure cognitive task should not involve any motor output, even no motor imagery, e.g. remembering a series of words. However, most of our daily activities comprise both motor and cognitive processes. Whether anticipation, preparation, and monitoring of movement are labeled as 'cognitive' or 'motor' functions seems a semantic issue.

To understand how (complex) movements are produced and what underlies movement disorders, integration of knowledge of cognitive and motor processes is warranted. Hereto, one should appreciate the intricacy of movement as well as cognition. For example, taking multiple steps is not the same as walking. Likewise, working memory consists of processes involved in encoding, storing, processing, and retrieving information. Thus, when a movement scientist studies actions that depend on cognitive control, it is essential to consider the specific cognitive processes involved in the motor task, rather than simply adding 'a secondary cognitive task'. For example, a dual task deficit can be caused by deficient inhibition processes or deficient set switching, besides the possibility

of increased attentional demands due to motor impairments. Similarly, for a cognitive scientist it should make a difference whether a task response is performed by the upper or lower limbs, or is a verbal response. For example, leg movements in upright position will introduce an additional task goal: maintaining balance.

The results of this thesis demonstrate that collaboration between scientists in the field of movement and in the field of cognition can be very fruitful. In **chapters 7 and 8** we used different types of set switching based on cognitive paradigms, helping us to reveal a specific deficit in PD patients with freezing of gait. Particularly in diseases that affect both cognitive and motor functions, close collaboration between experts of cognitive and movement sciences is valuable.

Strengths and limitations

Inherent in research, the studies presented in this thesis came with methodological strengths as well as limitations. As for the general strengths, we were able to include large samples of patients in the studies on PD, facilitating generalization of our findings to other patients with mild to moderate PD. Second, we used both experimental and clinical tests. The experimental tasks allowed a high sensitivity of outcome measures, whereas the clinical assessments were easy to use and clinically accepted. Another strength was that we looked beyond group means, aiming at identifying subgroups of patients who were (extra) vulnerable to falling. Finally, combining the study of gait and postural stability with well established cognitive task paradigms yielded new and potentially relevant insights that may help future development of diagnostic and therapeutic tools.

An important limitation was the inclusion of only mildly to moderately affected patient groups. All studies in this thesis required patients to walk independently, thereby restricting generalization of the results to patients with more severe gait disability. In PD, disease progression increasingly affects cognitive as well as motor functions, with involvement of cholinergic denervation in addition to dopamine deficiency.^{25,26} Hence, in more advanced disease stages, different interactions between cognition and movement probably originate from different neural substrates. Moreover, further cognitive decline can reduce the ability to use (cognitive) compensation strategies to enhance safe ambulation. In stroke, the type and severity of impairments depends heavily on the initial damage (i.e. integrity of the white matter tracts).²⁷⁻³¹ Hence, the effect of cognitive control processes on gait and balance can be very different when cognitive networks are affected in addition to motor impairments.

A second limitation was the sedentary nature of the PD cohorts in the studies in **chapters 4-6**. These studies were part of the large-scale ParkFit trial,³² a study

aiming at improving physical activity levels of patients with PD. In this large cohort we could prospectively monitor fall incidents over a long period, enabling the analysis of predictive factors. However, as discussed in **chapters 4 and 6**, the low physical activity levels in these patients at baseline limits generalization of our results to more active PD patients.

The third limitation is that we did not assess the effects of dopamine on (the interactions between) cognition, gait and postural stability. Dopamine replacement therapy improves bradykinetic and hypometric features of PD.³³ Amplitude and velocity of leg and arm movements increase as a function of dopamine treatment, which is potentially beneficial for gait and balance recovery.^{34,35} Dopamine also has an effect on freezing of gait episodes during “off” state.^{36,37} Moreover, certain types of set switching are sensitive to dopamine treatment. In contrast, the effect of dopamine on postural instability and falls is considered to be small to absent.³⁸ Consequently, when exploring basal ganglia functions that are involved in both motor and cognitive domains (such as action selection and motor learning), the effects of restoring dopamine levels in PD might prove to be insightful.

A final limitation meriting discussion is the ecologic validity of the motor tasks used in this study. Particularly when we aim to unravel the causes of falling in neurological patients, it would be valuable to also observe patients in their natural environments. Using unobtrusive instruments (e.g. small accelerometers) and videos capturing motions over prolonged periods in the home setting might add to our understanding of the mechanisms causing falls.³⁹⁻⁴¹

Future research perspectives

This thesis showed that different aspects of cognitive control impact on gait (attentional capacity), stepping (set switching) and fall risk (impulsivity) in patients post stroke and with PD. In this general discussion, I have implicitly touched upon different directions for future research on cognitive control over gait and postural stability. In this paragraph, I will discuss several options for future research.

Although we questioned the value of dual task assessment as a predictor of falls in PD (**chapter 4**), we also demonstrated that dual tasks can reveal gait problems that remain unnoticed in less demanding situations (**chapters 2 and 3**). There have been many studies investigating dual task effects on gait parameters in different neurological populations (reviewed in [42-45]). While the gait parameters in these previous studies are relatively uniform, the large variety of cognitive tasks that have been applied complicate direct comparison. A few studies investigated whether the type of concurrent cognitive task matters,

but these studies came up with inconclusive results.⁴⁶⁻⁴⁹ Using multiple cognitive tasks that tap different cognitive functions may help to understand whether dual task costs stem from a generalized attention deficit or from a specific cognitive deficit. To further increase our understanding of the mechanisms of dual tasking while walking, it would be valuable to explore which cognitive processes specifically interfere with gait. Hereto, I would recommend to use well established paradigms from experimental psychology that can distinguish, for instance, inhibition from working memory or learning. Moreover, differential effects of cognitive tasks can also be attributed to differences in the level of difficulty. An alternative is to manipulate the complexity within the same cognitive task, as we did in **chapter 4**.

In the different chapters of this thesis, multiple aspects of cognitive control have been related to gait and postural stability. Both for the stroke and the PD patients, there was supposedly a heterogeneous profile of cognitive deficits. In turn, this could have resulted in various interactions with gait and postural control. For instance, in the impulsive subgroup of PD patients (**chapter 6**), deficient inhibition control might have caused gait disability and fall risk. In **chapter 7**, I suggested that set switching interferes with gait in patients with PD as evidenced by switching deficits in the subgroup with freezing of gait. These results suggest that it might be useful to identify patients with specific cognitive deficits and assess their ability to walk and maintain stability in several conditions. The subgroup of PD patients with impulse control difficulty could, for example, be tested in a gait task requiring inhibition processes. Besides a better understanding of cognitive control of walking and postural stability, results from this type of studies might also provide helpful leads for therapy improvement.

In **chapters 7 and 8**, I observed that PD patients with freezing of gait responded differently compared to non-freezers. This finding was in line with previous studies showing that PD patients with freezing have specific cognitive deficits associated with frontostriatal functioning.⁵⁰⁻⁵² Other studies have associated freezing of gait with deficient integration of visual and motor information,⁵³ exaggerated postural preparation before step initiation,⁵⁴ and short-term change of a motor plan.⁵⁵ Moreover, freezing episodes are not restricted to gait, but also occur in upper limb movements and speech.^{56,57} As yet, a mechanistic explanation for freezing of gait is lacking.⁵⁸ Still, the specificity of the deficits in this subgroup might be regarded as evidence for a different underlying pathophysiology than in PD patients without freezing of gait.

Understanding of brain processes can be furthered using neuroimaging. Unfortunately, neuroimaging techniques are largely limited to upper-limb movements in a supine position. In an upright position, an additional motor task

is to keep the body stable within the base of support, complicating the translation of findings from upper-limb neuroimaging studies to the situations where the human body is erect. Still, there are some options to record brain activity related to gait and stepping. First, cortical activity during standing and stepping can be recorded using EEG.⁵⁹⁻⁶¹ This technique is useful to study preparatory activity (contingent negative variation) and can perhaps also be used to assess error-related activity in postural perturbations. A downside of EEG is that its sensitivity is restricted to the cortex. A second technique is functional MRI (fMRI), which has a higher spatial resolution and can also be used to measure subcortical activity. Although gait assessment using fMRI is still limited to motor imagery tasks,⁶²⁻⁶⁴ fMRI studies in resting state, while performing finger movements, and using a virtual-reality gait paradigm have yielded interesting results with regard to freezing of gait.⁶⁴⁻⁶⁶ Finally, some studies have used deep brain stimulation of the pedunculopontine nucleus, subthalamic nucleus and/or globus pallidus, allowing to explore the role of these specific structures in parkinsonian gait.⁶⁷⁻⁶⁹

References

1. Baddeley AD. *Working memory*. Oxford Oxfordshire New York: Clarendon Press; Oxford University Press; 1986.
2. Kahneman D. *Attention and task interference*. In: Kahneman D, ed. *Attention and Effort*. Englewood-Cliffs, New Jersey: Prentice-Hall; 1973:178-201.
3. Adcock RA, Constable RT, Gore JC, Goldman-Rakic PS. Functional neuroanatomy of executive processes involved in dual-task performance. *Proc Natl Acad Sci U S A*. Mar 28 2000;97(7):3567-72.
4. Bunge SA, Klingberg T, Jacobsen RB, Gabrieli JD. A resource model of the neural basis of executive working memory. *Proc Natl Acad Sci U S A*. Mar 28 2000;97(7):3573-8.
5. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. *Nature*. Nov 16 1995;378(6554):279-81.
6. Planton M, Peiffer S, Albucher JF, et al. Neuropsychological outcome after a first symptomatic ischaemic stroke with 'good recovery'. *Eur J Neurol*. Feb 2012;19(2):212-9.
7. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*. 2005;65(8):1239-45.
8. Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci*. 2006;248(1-2):196-204.
9. Kelly VE, Eusterbrock AJ, Shumway-Cook A. The effects of instructions on dual-task walking and cognitive task performance in people with Parkinson's disease. *Parkinson's disease*. 2012;2012:671261.
10. Keus SH, Hendriks HJ, Bloem BR, et al. KNGF-richtlijn Ziekte van Parkinson. *Nederlands Tijdschrift voor Fysiotherapie*. 2004;114(3).
11. Brauer SG, Woollacott MH, Lamont R, et al. Single and dual task gait training in people with Parkinson's disease: a protocol for a randomised controlled trial. *BMC Neurol*. 2011;11:90.
12. Mirelman A, Rochester L, Reelick M, et al. V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. *BMC Neurol*. 2013;13:15.
13. Nieuwboer A. Dual Task Practice in Parkinson's Disease (Duality-PD). *ClinicalTrials.gov* [Internet] 2011; <http://clinicaltrials.gov/show/NCT01375413>.
14. Plummer-D'Amato P, Kyvelidou A, Sternad D, Najafi B, Villalobos RM, Zurakowski D. Training dual-task walking in community-dwelling adults within 1 year of stroke: a protocol for a single-blind randomized controlled trial. *BMC Neurol*. 2012;12:129.
15. Wylie SA, van den Wildenberg W, Ridderinkhof KR, Claassen DO, Wooten GF, Manning CA. Differential susceptibility to motor impulsivity among functional subtypes of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. Aug 23 2012.
16. Bowen FP, Kamienny RS, Burns MM, Yahr M. Parkinsonism: effects of levodopa treatment on concept formation. *Neurology*. Aug 1975;25(8):701-4.
17. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function

- in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*. Dec 2001;11(12):1136-43.
18. Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*. Dec 2001;124(Pt 12):2503-12.
 19. Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia*. 1989;27(11-12):1329-43.
 20. Hayes AE, Davidson MC, Keele SW, Rafal RD. Toward a functional analysis of the basal ganglia. *J Cogn Neurosci*. 1998;10(2):178-98.
 21. Owen AM, James M, Leigh PN, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain*. 1992;115 (Pt 6):1727-51.
 22. Rogers RD, Sahakian BJ, Hodges JR, Polkey CE, Kennard C, Robbins TW. Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain*. May 1998;121:815-42.
 23. Monsell S. Task switching. *Trends in cognitive sciences*. Mar 2003;7(3):134-40.
 24. Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci*. May 29 2007;362(1481):917-32.
 25. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol*. Dec 2010;9(12):1200-13.
 26. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009;132(Pt 11):2958-69.
 27. Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. *Brain*. May 2011;134(Pt 5):1264-76.
 28. Hendricks HT, van Limbeek J, Geurts AC, Zwartz MJ. Motor recovery after stroke: a systematic review of the literature. *Arch Phys Med Rehabil*. Nov 2002;83(11):1629-37.
 29. Page SJ, Gauthier LV, White S. Size Doesn't Matter: Cortical Stroke Lesion Volume Is Not Associated With Upper Extremity Motor Impairment and Function in Mild, Chronic Hemiparesis. *Arch Phys Med Rehabil*. Jan 18 2013.
 30. Riley JD, Le V, Der-Yeghiaian L, et al. Anatomy of stroke injury predicts gains from therapy. *Stroke*. Feb 2011;42(2):421-6.
 31. Zhu LL, Lindenberg R, Alexander MP, Schlaug G. Lesion load of the corticospinal tract predicts motor impairment in chronic stroke. *Stroke*. May 2010;41(5):910-5.
 32. Van Nimwegen M, Speelman AD, Overeem S, et al. Promotion of physical activity and fitness in sedentary patients with Parkinson's disease: randomised controlled trial. *BMJ*. 2013;346:f576.
 33. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology*. May 26 2009;72(21 Suppl 4):S1-136.
 34. Frank JS, Horak FB, Nutt J. Centrally initiated postural adjustments in parkinsonian patients on and off levodopa. *J Neurophysiol*. Nov 2000;84(5):2440-8.

35. Rochester L, Baker K, Nieuwboer A, Burn D. Targeting dopa-sensitive and dopa-resistant gait dysfunction in Parkinson's disease: selective responses to internal and external cues. *Mov Disord.* Feb 15 2011;26(3):430-5.
36. Giladi N. Medical treatment of freezing of gait. *Mov Disord.* 2008;23 Suppl 2:S482-8.
37. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur J Neurol.* Jul 2003;10(4):391-8.
38. Bohnen NI, Muller ML, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology.* Nov 17 2009;73(20):1670-6.
39. Kavanagh JJ, Menz HB. Accelerometry: a technique for quantifying movement patterns during walking. *Gait Posture.* Jul 2008;28(1):1-15.
40. Robinovitch SN, Feldman F, Yang Y, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet.* Jan 5 2013;381(9860):47-54.
41. Maetzler W, Domingos J, Srujies K, Ferreira JJ, Bloem BR. Quantitative wearable sensors for objective assessment of Parkinson's disease. *Mov Disord.* Oct 2013;28(12):1628-37.
42. Al-Yahya E, Dawes H, Smith L, Dennis A, Howells K, Cockburn J. Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* Jan 2011;35(3):715-28.
43. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? *Eur J Neurol.* Jul 2009;16(7):786-95.
44. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc.* Nov 2012;60(11):2127-36.
45. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-42.
46. Beauchet O, Dubost V, Aminian K, Gonthier R, Kressig RW. Dual-task-related gait changes in the elderly: does the type of cognitive task matter? *J Mot Behav.* 2005;37(4):259-64.
47. Beauchet O, Dubost V, Gonthier R, Kressig RW. Dual-task-related gait changes in transitionally frail older adults: the type of the walking-associated cognitive task matters. *Gerontology.* 2005;51(1):48-52.
48. Haggard P, Cockburn J, Cock J, Fordham C, Wade D. Interference between gait and cognitive tasks in a rehabilitating neurological population. *J Neurol Neurosurg Psychiatry.* 2000;69(4):479-86.
49. Plummer-D'Amato P, Altmann LJ, Saracino D, Fox E, Behrman AL, Marsiske M. Interactions between cognitive tasks and gait after stroke: a dual task study. *Gait Posture.* May 2008;27(4):683-8.
50. Amboni M, Cozzolino A, Longo K, Picillo M, Barone P. Freezing of gait and executive functions in patients with Parkinson's disease. *Mov Disord.* Feb 15 2008;23(3):395-400.
51. Ferraye MU, Ardouin C, Lhommee E, et al. Levodopa-Resistant Freezing of Gait and Executive Dysfunction in Parkinson's Disease. *Eur Neurol.* Feb 27 2013;69(5):281-8.
52. Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of

- gait in Parkinson's disease. *Mov Disord.* Jun 15 2010;25(8):1000-4.
53. Cowie D, Limousin P, Peters A, Day BL. Insights into the neural control of locomotion from walking through doorways in Parkinson's disease. *Neuropsychologia.* Jul 2010;48(9):2750-7.
54. Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. *Exp Neurol.* Feb 2009;215(2):334-41.
55. Knobl P, Kielstra L, Almeida Q. The relationship between motor planning and freezing of gait in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* Jan 2012;83(1):98-101.
56. Giladi N, McMahon D, Przedborski S, et al. Motor blocks in Parkinson's disease. *Neurology.* Feb 1992;42(2):333-9.
57. Nieuwboer A, Vercruysse S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. *Eur J Neurosci.* Apr 2009;29(7):1422-30.
58. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* Aug 2011;10(8):734-44.
59. Adkin AL, Campbell AD, Chua R, Carpenter MG. The influence of postural threat on the cortical response to unpredictable and predictable postural perturbations. *Neurosci Lett.* Apr 18 2008;435(2):120-5.
60. Adkin AL, Quant S, Maki BE, McIlroy WE. Cortical responses associated with predictable and unpredictable compensatory balance reactions. *Exp Brain Res.* Jun 2006;172(1):85-93.
61. Jacobs JV, Fujiwara K, Tomita H, Furune N, Kunita K, Horak FB. Changes in the activity of the cerebral cortex relate to postural response modification when warned of a perturbation. *Clin Neurophysiol.* Jun 2008;119(6):1431-42.
62. Bakker M, De Lange FP, Helmich RC, Scheeringa R, Bloem BR, Toni I. Cerebral correlates of motor imagery of normal and precision gait. *Neuroimage.* Jul 1 2008;41(3):998-1010.
63. Bakker M, de Lange FP, Stevens JA, Toni I, Bloem BR. Motor imagery of gait: a quantitative approach. *Exp Brain Res.* May 2007;179(3):497-504.
64. Snijders AH, Leunissen I, Bakker M, et al. Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. *Brain.* Jan 2011;134(Pt 1):59-72.
65. Shine JM, Matar E, Ward PB, et al. Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease. *Brain.* Apr 2013;136(Pt 4):1204-15.
66. Vercruysse S, Spildooren J, Heremans E, et al. The Neural Correlates of Upper Limb Motor Blocks in Parkinson's Disease and Their Relation to Freezing of Gait. *Cereb Cortex.* Jul 16 2013.
67. Thevathasan W, Cole MH, Graepel CL, et al. A spatiotemporal analysis of gait freezing and the impact of pedunculopontine nucleus stimulation. *Brain.* May 2012;135(Pt 5):1446-54.
68. Thevathasan W, Pogosyan A, Hyam JA, et al. Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. *Brain.* Jan 2012;135(Pt 1):148-60.

69. Rocchi L, Carlson-Kuhta P, Chiari L, Burchiel KJ, Hogarth P, Horak FB. Effects of deep brain stimulation in the subthalamic nucleus or globus pallidus internus on step initiation in Parkinson disease. *J Neurosurg*. Oct 5 2012;117(6):9.

Nederlandse samenvatting

Het doel van dit proefschrift was om de rol van cognitieve controle bij lopen en balans beter te begrijpen, zowel voor patiënten na een cerebrovasculair accident (CVA: herseninfarct of hersenbloeding) als voor patiënten met de ziekte van Parkinson (ZvP). CVA en de ZvP zijn aandoeningen die complementair zijn wat betreft het begin van de ziekte en het ziekteverloop. Een CVA treedt plotseling op en leidt tot acute symptomen. Met name in de eerste maanden na een CVA kunnen patiënten aanzienlijke vooruitgang boeken. De ZvP is daarentegen progressief van aard, waarbij de ernst van de symptomen toeneemt naarmate de ziekte vordert.

In het eerste deel van mijn proefschrift heb ik de automaticiteit van complexe loopvaardigheden van patiënten met een CVA gemeten, en bestudeerd of deze automaticiteit verbeterd kan worden door te trainen. De looptaak die we daarvoor gebruikten bestond uit het ontwijken van obstakels terwijl patiënten op een lopende band liepen. Om te testen hoeveel aandacht nodig was voor deze looptaak, lieten we patiënten tegelijkertijd een auditieve cognitieve taak uitvoeren (Stroop-taak). Door de prestatie op de looptaak en de cognitieve taak in isolatie (enkeltaak) te vergelijken met de prestatie wanneer de taken tegelijkertijd werden uitgevoerd (dubbeltaak), konden we de dubbeltaakkosten van beide taken meten (maat voor automaticiteit: het verschil tussen de enkel- en dubbeltaakprestatie). In **hoofdstuk 2** zag ik dat de prestatie op de obstakeltaak verslechterde wanneer de Strooptaak tegelijkertijd werd uitgevoerd. Deelnemers waren minder succesvol in het ontwijken van de obstakels en de spierreactie was vertraagd. Dit dubbeltaakeffect op de looptaak was vergelijkbaar voor patiënten met een CVA en gezonde controles. Op de cognitieve taak was wel een verschil in dubbeltaakeffecten zichtbaar tussen de twee groepen. Patiënten met een CVA presteerden slechter dan gezonde proefpersonen op de cognitieve taak als ze tegelijkertijd een obstakel moesten vermijden. Deze bevindingen suggereren dat patiënten met een CVA meer aandacht nodig hebben om te voorkomen dat ze struikelen tijdens het vermijden van obstakels. Hierbij gaven ze prioriteit aan de looptaak ('posture first' strategie). Dit lijkt een wijze strategie: Fouten maken tijdens het vermijden van obstakels kunnen immers ernstigere gevolgen hebben, zoals struikelen en vallen, dan fouten in een cognitieve taak.

In **hoofdstuk 3** onderzochten we het effect van een training die als doel had om het vermogen om stapaanpassingen te doen tijdens lopen bij patiënten met een CVA. Hiervoor gebruikten we dezelfde taken als in hoofdstuk 2. De interventie bestond uit 10 trainingssessies. Daarbij werd gebruik gemaakt van een geïnstrumenteerde loopband waarop visuele cues werden geprojecteerd die dienden als doel voor de voetplaatsing, of als obstakel dat ontweken moest

worden. De prestatie op de obstakeltaak voor en na de training werd vergeleken, zowel voor de enkel- als de dubbeltaak. Patiënten met een CVA werden beter in het ontwijken van obstakels na de training. Naast dit effect zagen we na de training een betere prestatie bij het dubbeltaken: De prestatie op de Strooptaak terwijl tegelijkertijd een obstakel moest worden vermeden, werd 5% beter. De dubbeltaakkosten voor en na de training verschilden echter niet van elkaar. Hoewel een controlegroep ontbrak in dit onderzoek, suggereren deze resultaten dat het vermogen om stapaanpassingen uit te voeren trainbaar is voor patiënten in de chronische fase na een CVA. Dit trainingseffect was gerelateerd aan een verminderde behoefte om aandacht aan de looptaak te besteden.

In het tweede deel van dit proefschrift lag de focus op cognitieve controle over lopen en balans bij patiënten met de ZvP. Ten eerste heb ik de hypothese getoetst die stelt dat problemen met dubbeltaken het valrisico van patiënten met de ZvP vergroot (**hoofdstuk 4**). Het idee van deze hypothese is dat patiënten met de ZvP moeite hebben om de aandacht te richten op lopen en balanshandhaving wanneer ze met meerdere taken tegelijk bezig zijn. Als patiënten de zogenaamde “posture second” strategie zouden gebruiken, zou dat kunnen leiden tot gevaarlijke situaties, en uiteindelijk resulteren in een val. In dit hoofdstuk zijn de dubbeltaakkosten op loopparameters (zonder obstakels) en op de auditieve Strooptaak gemeten en vergeleken tussen patiënten die wel of niet meerdere keren vielen. Tegen de verwachting in waren er geen verschillen in dubbeltaakkosten tussen deze valgroepen op de looptaak en op de cognitieve taak. Omdat op basis van deze bevinding niet uitgesloten kan worden dat vailleurs een posture second strategie hanteerden, heb ik ook de individuele dubbeltaakkosten op beide taken geanalyseerd. Deze analyse liet zien dat patiënten met meerdere valincidenten geen andere strategieën gebruikten dan de patiënten die niet of een keer vielen. Uit deze resultaten samen concludeerden we dat het meten van dubbeltaakprestatie geen klinisch valide methode is om het valrisico van patiënten met de ZvP te voorspellen. Klinische maten (zoals ernst van de motorische symptomen) en loopparameters tijdens de enkeltaak waren betere voorspellers dan dubbeltaakkosten.

Het dubbeltaakparadigma stelt ons in staat om de benodigde hoeveelheid cognitieve hulpbronnen te schatten. Dit leert ons echter niet *welke* cognitieve functies betrokken zijn bij motorische taken. In het onderzoek in **hoofdstuk 5**, heb ik cognitieve controle over motorische taken gespecificeerd door de vier belangrijkste componenten te meten: werkgeheugen, set switching, inhibitie en responsgeneratie. Het doel van dit onderzoek was om de relatie tussen deze cognitieve componenten en de volgende motorische componenten te

bestuderen: de Timed Up and Go (TUG) test en PIGD (posturale instabiliteit en loopbeperkingen) scores van de UPDRS-III. Werkgeheugen en responsgeneratie vertoondeneenzwakke,maarsignificante correlatiemetdeTUGtestenmetdePIGD score. Wanneer we controleerden voor ziekte-ernst, leeftijd en opleidingsniveau bleef alleen de correlatie tussen de TUG test en responsgeneratie (semantische fluency) significant. Geen van de cognitieve testen was een onafhankelijke voorspeller van PIGD wanneer werd gecontroleerd voor ziekte-ernst, leeftijd en opleidingsniveau. Dit onderzoek suggereert dat responsgeneratie en, in minder mate, werkgeheugen betrokken kunnen zijn bij functionele loop- en balanstaken.

Het onderwerp in **hoofdstuk 7 en 8** was het vermogen van patiënten met de ZvP om te schakelen tussen cognitieve en motorische sets (set switching). De ZvP tast het vermogen aan om flexibel te schakelen tussen motorische reeksen of tussen cognitieve regels. Het is echter onduidelijk of problemen met set switching bijdragen aan motorische symptomen van patiënten met de ZvP zoals bradykinesie en akinesie (traagheid van bewegen en bewegingsarmoede). Onze hypothese was dat set switching problemen het initiëren van een stap zou bemoeilijken, zoals te zien is bij problemen met het starten van lopen tijdens freezing episodes. Om deze hypothese te toetsen heb ik een paradigma ontworpen waarbij stapinitiatie en set switching geïntegreerd werden in een taak. In dit experiment kon set switching in het motorische domein direct vergeleken worden met switching in het cognitieve domein (**hoofdstuk 7**). De deelnemers moesten een stap vooruit of achteruit zetten als reactie op een figuur die ze zagen op een computerscherm voor hen. Een motorische switch definieerden we als een verandering in de staprichting in elkaar opvolgende trials. Een cognitieve switch definieerden we als een verandering in het relevante kenmerk van de figuur (kleur of vorm). De resultaten lieten geen motorische of cognitieve switch-beperking zien voor patiënten met de ZvP ten opzichte van gezonde proefpersonen. De patiënten met freezing of gait hadden echter een significante beperking tijdens motorische, maar niet tijdens cognitieve set switching. Deze resultaten suggereren dat problemen met motorische set switching ook bij stappen voorkomen, en mogelijk bijdragen aan het optreden van freezing of gait episodes bij patiënten met de ZvP.

Om de invloed van set switching op stapreacties bij patiënten met de ZvP verder te onderzoeken, keken we in **hoofdstuk 8** of switching een negatieve invloed heeft op stappen in reactie op een verstoring. De proefpersonen moesten reageren op een beweging van een platform waarop ze stonden (translatie). Bij een grote translatie was het nodig om een stap te zetten om de balans te handhaven. Bij een kleine translatie was een “feet-in-place” reactie (dus: geen stap) voldoende. We pasten twee condities toe: in de “no switch” conditie

volgde de stap op een serie van andere stap-uitlokkende verstoringen. In deze conditie was de verstoring die de stap uitlokte dus onderdeel van een serie met identieke verstoringen. Hierdoor kon de proefpersoon de ervaring van de voorgaande trials gebruiken en het posturele systeem zodanig instellen dat de respons geoptimaliseerd werd (posturale set). In de “switch” conditie, volgde de stap op een serie van verstoringen waarbij een feet-in-place reactie volstond. De proefpersoon moest dus switching van een feet-in-place strategie naar een staprespons. Alle proefpersonen hadden slechtere stapkenmerken in switch trials dan in no switch trials: de been- en romphoeken waren minder gunstig proefpersonen hadden meer stappen nodig om de balans te herstellen dan in de no switch trials. De belangrijkste bevinding van dit onderzoek was echter dat dit effect van posturele set vergelijkbaar was tussen patiënten met de ZvP en gezonde proefpersonen. Zowel bij patiënten met, als bij patiënten zonder freezing of gait, zagen we geen switchbeperking die balansherstellende stappen verslechterde. Een interessante observatie was dat freezers meer moeite hadden om hun stapreacties te verbeteren binnen een serie van stappen. Dit duidt op meer moeite om de staprespons aan te passen op basis van de ervaring opgedaan tijdens eerdere, identieke trials. Deze beperking in motoradaptatie kan onze bevindingen ten aanzien van switcheffecten verstoord hebben

Dankwoord

Een boek met mijn naam op de voorkant, dat bestond nog niet. U heeft het waarschijnlijk van a tot z met volle aandacht gelezen. Hoewel ik veel denk- en doewerk in dit proefschrift heb gestopt, is het geheel op vele fronten mogelijk gemaakt en beïnvloed door anderen. In de methode, de data, en de interpretaties klinken de stemmen van vele anderen door.

Allereerst hoorde u een koor van honderden mensen doorklinken in de data. Zonder gegevens geen empirie, dus geen wetenschappelijk onderzoek. Vele patiënten en gezonde personen waren bereid om mee te doen aan de testen die wij voor jullie bedacht hadden. Jullie welwillendheid was verwarmend! Zeer veel dank voor jullie bijdrage. Ik hoop dat het jullie allen goed gaat.

Tjeerd de Jong: Je staat hier vast en zeker liever niet zo vooraan, maar dat heb je toch echt over jezelf afgeroepen. Je hebt me de ruimte gegeven om mijn ambitie te volgen en gestimuleerd om uitdagingen aan te gaan. Ik weet dat dat volgens jou de normaalste zaak van de wereld is, maar dat maakt het niet minder prettig. Het was ontzettend fijn om een 'baas' te hebben met een groot hart voor de inhoud van ons vak.

Mijn promotoren, Bas Bloem en Sander Geurts: Jullie hebben mij veel ruimte gelaten om het onderzoek op te zetten zoals ik dacht dat goed was. De ideeën hierin zijn sterk geïnspireerd door jullie beider visies op bewegen en de sturing daarvan. Bas, ik heb me op je 'oude' geliefde vakgebied begeven in dit proefschrift door in te gaan op lopen, balans, en cognitie bij PD. Ik hoop van harte dat je naast al je activiteiten om de zorg te vernieuwen, ook actief blijft op dit onderwerp. Wie weet kruisen onze wegen dan nog eens? Sander, fijn dat je altijd tussendoor wel een gaatje wist te vinden om belangrijke beslissingen af te stemmen en dank dat je op tijd aan de bel trok als ik leek te verdwijnen tussen de verschillende afdelingen en alle betrokken auteurs.

Rianne Esselink (co-promotor): In ons eerste overlegje met Marten erbij, kwam je binnenvliegen in je witte jas, plofte neer op een stoel, krabbelde onleesbare tekens op een kladblokje... Ik was onder de indruk van je actie en dacht dat dat wel goed moest komen met ons. Dat kwam het ook. Je hebt me ontzettend veel laten zien en verteld over de neurologische patiëntenpopulatie. Stuk voor stuk case studies, zodat ik nu van alles weet over DBS, cognitie, en psychiatrie. Behalve dat onze interacties erg helpend waren voor dit proefschrift, waren ze ook vaak gezellig en met oog voor de menselijke kant van de zaak. Laat dat DBS-centrum er maar komen, je weet me te vinden...

Bert de Swart (co-promotor): Jij haalde me naar de overkant, de Kapittelweg over. Dank daarvoor! Ik heb gemerkt hoe sterk je bent in het zien van kansen, en dat ook daadwerkelijk ten uitvoer brengen. Hierdoor heb je niet alleen dit

proefschrift maar ook vele andere projecten (mede-)mogelijk gemaakt.

Vivian Weerdesteyn: Je hebt geen officiële rol in de mijn promotie, maar daar is dan ook alles mee gezegd. Jouw rol in mijn onderzoek was groot doordat je me wegwijs hebt gemaakt in de loop- en balanstaken van de eerste hoofdstukken, en later kritisch met me meedacht over de overige taken. Fijn dat je altijd redeneert vanuit het mechanisme (helaas houdt de data zich niet altijd aan onze theorieën) en kritisch blijft kijken en zoeken of we niks over het hoofd hebben gezien.

Roshan Cools: Mijn kennis van jouw vakgebied was een jaar of 5 geleden beperkt tot Pavlov en Skinner. Het repertoire is inmiddels aardig uitgebreid, zeker dankzij jou. Daarnaast maakten je vragen en opmerkingen dat ik scherper moest, en ook ben gaan kijken naar de opzet van onderzoek. Dank je wel dat je met me mee wilde denken, ook over een eventueel vervolg na deze promotie!

Roy Kessels: De tweede persoon die me heeft geholpen bij het thuisraken in het cognitieve deel van mijn proefschrift. Je hebt me wegwijs gemaakt in de neuropsychologische taken van dit proefschrift. En je was de stuwende kracht achter hoofdstuk 4, dat volgens jou toch gewoon gepubliceerd moest worden.

Marten Munneke: Na een jaartje werken bij revalidatie, haalde jij me binnen bij neurologie. Een zilveren ParkFit-Porsche was jullie lokkertje om een promotietraject binnen ParkFit te gaan doen. Gelukkig geef ik heel weinig om auto's (het werd een oud, wit Citroëntje), maar des te meer om een dynamisch, enthousiast team met een missie.

Dan was er nog een leger aan mensen die me tussendoor hebben bijgestaan. Zoals George Borm en Rogier Donders, die waardevolle suggesties gaven om mijn statistische ideeën te verbeteren en niet onbelangrijk, het onderzoeksvoorstel op statistische gronden door de medisch-ethische toetsing te krijgen. Zoals Roland Loeffen, die me hielp bij het implementeren van de verschillende taken en registratie daarvan in het lab, en het geheel weer aan de praat te krijgen als het even niet meer wilde. Zoals de Parkinson-verpleegkundigen Martha Huvenaars en Jacqueline Deenen en alle neurologen die hebben gezorgd dat er zoveel patiënten in ons onderzoek mee wilden doen. Zoals alle onderzoeksassistenten (Marije, Tia, Willeke, Karin, Anita, Thijs, José, Ine), tientallen HAN-stagiaires en RU-stagiaires (met name Bart, Lyvonne en Eline) die binnen het ParkFit-team ontelbaar veel vragenlijsten, cognitieve testen en valregistraties hebben afgenomen. And like Aner Weiss, who carried out the additional analyses of chapter 5. Applaus!

Voor mij is het onmogelijk om te werken zonder wandelgangenoverlegjes en koffie-onderbrekingen. En daarvoor heb je collega's nodig (patiënten in de wachtkamer zaten daar toch minder op te wachten). Dank dus voor jullie gezelligheid en ontvangst in jullie kamers, lieve onderzoekers van de

revalidatie-gang en loslopende neurologie-onderzoekers. Bij naam moet ik dan wel een paar van jullie specifiek noemen: Roos, voor je samenwerking resulterend in H2. Jorik, Lars en Digna, voor het uitwisselen van ideeën en resultaten van Parkinsononderzoek (en de soms hilarische eetmomenten). De ParC-onderzoekers, ons groepje dat met uitsterven werd bedreigd ondanks de bindende salsa-bijeenkomsten en (afscheid-)borrels. Roomies Marjolein en Esther, ik kon aan het eind van de gang al horen of jullie er waren... Lekker met de voetjes in de ventilatorstroom, boer zoekt vrouw in een minuut, rariteiten van niet-nader-te noemen anderen bespreken. En dank voor de gezelligheid verzorgd door mijn HAN Sport & Bewegen collega's, die jarenlang konden horen dat het alweer vrijdag was.

Van het eerste uur, Marlies en Arlène: Ik heb al eerder diep mijn hoed afgenomen voor wat jullie hier voor elkaar gebokst hebben. Er is zoiets als een gat tussen een fantastisch plan en de daadwerkelijke uitvoering, dacht ik altijd. Niet bij jullie en ik heb daarvan mogen profiteren. Met pit (Arlène) en reflectie (Marlies) als belangrijke ingrediënten, om maar even lekker kort door de bocht te gaan. Is het dansje af? Pakjes genaaid?

Paranimf (van beroep) Mark: Ik kom maar niet van jou af. En ok, jij ook niet van mij. Gelukkig maar, want een vriend op wiens professionele idee je kunt vertrouwen is zeer waardevol. Je bent een kei in het kritisch bevragen van de basisidee van een onderzoek en de daarbij behorende opzet. Dat is je inhoudelijke bijdrage hier. Dan is er nog je vorm-bijdrage in de lay-out van dit boekje. En dan moet je me ook nog eens bijstaan (achter-staan) op het moment suprême. Succes!

Lieve broer en zusjes: Het is heerlijk om in jullie midden te verkeren met al jullie diversiteit en flauwe grappen. Never a dull moment. Maar ook een cluppie om op terug te vallen als dat nodig is. Hoewel het woord volgens mama ongepast is, ik ben ontzettend trots op jullie. Onze benjamin Sofie staat me zelfs bij vanmiddag als paranimf.

Lieve papa, het is niks voor mij om een publieke tekst te schrijven die de geadresseerde zelf niet kan lezen. Mijn promotietraject heeft parallel gelopen aan het begin en einde van jouw ziekte, alleen was het verloop tegengesteld. Lieve mama, jouw en papa's bijdrage aan dit proefschrift is er overduidelijk maar moeilijk aan te wijzen. In ieder geval zijn er veel eigenschappen in mij die ik van jullie herken en die mij hier hebben gebracht. Jullie levenswijze is de basis voor wat ik doe en wat ik nu kan. Dank je wel voor alles!

Lieve Eline, het leven is top samen met jou. Dank je wel voor je lichtheid, flexibiliteit en plezier. En voor Fiene, onze vrolijke boef! Fiene, ik leg je nog wel een keer uit waar dit allemaal over ging.

Curriculum vitae



Katrijn Smulders was born in 1978 in Eindhoven, the Netherlands. After finishing her secondary education at the Lorentz Lyceum in Eindhoven in 1997, she started her research education studying Human Movement Sciences at the Vrije Universiteit in Amsterdam. Here she performed a lab study on force-velocity characteristics of the rat gastrocnemius muscle (supervisor prof. Arnold de Haan) and conducted a literature study on chronic instability of the ankle. During an research internship at TNO Industry, she investigated shock absorption of soccer shoes on new artificial turf (supervisor dr. Jos de Koning). Katrijn graduated in 2001. Her first job was at Winnock rehabilitation services as exercise coach. In 2003, Katrijn started as a lecturer and researcher at the HAN University of Applied Sciences at the Institute of Sports and Exercise Studies. In 2008, she joined the research group Neurorehabilitation of lector dr. Bert de Swart at the HAN, and started a research project at the department of Rehabilitation of the Radboud University Medical Centre under supervision of dr. Vivian Weerdesteyn and prof. Alexander Geurts. This was the starting point for her PhD trajectory in 2009, which was a collaboration between the departments of Neurology and Rehabilitation under supervision of profs. Bastiaan Bloem and Alexander Geurts. Katrijn obtained a scholarship from the HAN for the first part of her PhD work, and a grant from the Stichting International Parkinson Foundation to conduct the second part. Alongside her PhD research projects, Katrijn continued her work as a lecturer at the HAN. Katrijn is married to Eline and, since October 2013, mother of Fiene.

List of publications

Smulders K, Esselink RA, Cools R, Bloem BR. Trait impulsivity is associated with the risk of falls in Parkinson's disease. *PLoS One*. 2014;9(3):e91190.

Smulders K, Esselink RA, De Swart BJ, Geurts AC, Bloem BR, Weerdesteyn V. Postural inflexibility in PD: Does it affect compensatory stepping? *Gait Posture*. 2014;39(2):700-6.

Nonnekens J, Scotti A, Oude Nijhuis L, **Smulders K**, Queralt A, Geurts AC, Bloem BR, Weerdesteyn V. Are postural responses to backward and forward perturbations processed by different neural circuits? *Neuroscience*. 2013;245:109-20.

Van Nimwegen M, Speelman AD, Overeem S, Van de Warrenburg BP, **Smulders K**, Dontje ML, Borm GF, Backx FJ, Bloem BR, Munneke M. Promotion of physical activity and fitness in sedentary patients with Parkinson's disease: randomised controlled trial. *BMJ* 2013;346:f576.

Smulders K, van Nimwegen M, Munneke M, Bloem BR, Kessels RP, Esselink RA. Involvement of specific executive functions in mobility in Parkinson's disease. *Parkinsonism Rel Disord*. 2013;19(1):126-8.

Smulders K, van Swigchem R, de Swart BJ, Geurts AC, Weerdesteyn V. Community-dwelling people with chronic stroke need disproportionate attention while walking and negotiating obstacles. *Gait Posture*. 2012;36(1):127-32.

Smulders K, Esselink RA, Weiss A, Kessels RP, Geurts AC, Bloem BR. Assessment of dual tasking has no clinical value for fall prediction in Parkinson's disease. *J Neurol*. 2012;259(9):1840-7.

Van Nimwegen M, Speelman AD, **Smulders K**, Overeem S, Borm GF, Backx FJ, Bloem BR, Munneke M. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. *BMC Neurol*. 2010;10(1):70.

Donders Graduate School for Cognitive Neuroscience Series

1. Van Aalderen-Smeets, S.I. (2007). *Neural dynamics of visual selection*. Maastricht University, Maastricht, the Netherlands.
2. Schoffelen, J.M. (2007). *Neuronal communication through coherence in the human motor system*. Radboud University Nijmegen, Nijmegen, the Netherlands.
3. De Lange, F.P. (2008). *Neural mechanisms of motor imagery*. Radboud University Nijmegen, Nijmegen, the Netherlands.
4. Grol, M.J. (2008). *Parieto-frontal circuitry in visuomotor control*. Utrecht University, Utrecht, the Netherlands.
5. Bauer, M. (2008). *Functional roles of rhythmic neuronal activity in the human visual and somatosensory system*. Radboud University Nijmegen, Nijmegen, the Netherlands.
6. Mazaheri, A. (2008). *The influence of ongoing oscillatory brain activity on evoked responses and behaviour*. Radboud University Nijmegen, Nijmegen, the Netherlands.
7. Hooijmans, C.R. (2008). *Impact of nutritional lipids and vascular factors in Alzheimer's disease*. Radboud University Nijmegen, Nijmegen, the Netherlands.
8. Gaszner, B. (2008). *Plastic responses to stress by the rodent urocortinergic Edinger-Westphal nucleus*. Radboud University Nijmegen, Nijmegen, the Netherlands.
9. Willems, R.M. (2009). *Neural reflections of meaning in gesture, language and action*. Radboud University Nijmegen, Nijmegen, the Netherlands.
10. Van Pelt, S. (2009). *Dynamic neural representations of human visuomotor space*. Radboud University Nijmegen, Nijmegen, the Netherlands.
11. Lommertzen, J. (2009). *Visuomotor coupling at different levels of complexity*. Radboud University Nijmegen, Nijmegen, the Netherlands.
12. Poljac, E. (2009). *Dynamics of cognitive control in task switching: Looking beyond the switch cost*. Radboud University Nijmegen, Nijmegen, the Netherlands.
13. Poser, B.A. (2009). *Techniques for BOLD and blood volume weighted fMRI*. Radboud University Nijmegen, Nijmegen, the Netherlands.
14. Baggio, G. (2009). *Semantics and the electrophysiology of meaning. Tense, aspect, event structure*. Radboud University Nijmegen, Nijmegen, the Netherlands.
15. Van Wingen, G.A. (2009). *Biological determinants of amygdala functioning*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
16. Bakker, M. (2009). *Supraspinal control of walking: Lessons from motor imagery*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
17. Aarts, E. (2009). *Resisting temptation: The role of the anterior cingulate cortex in adjusting cognitive control*. Radboud University Nijmegen, Nijmegen, the Netherlands.
18. Prinz, S. (2009). *Waterbath stunning of chickens – Effects of electrical parameters on the electroencephalogram and physical reflexes of broilers*. Radboud University Nijmegen, Nijmegen, the Netherlands.
19. Knippenberg, J.M.J. (2009). *The N150 of the Auditory Evoked Potential from the rat amygdala: In search for its functional significance*. Radboud University Nijmegen, Nijmegen, the Netherlands.
20. Dumont, G.J.H. (2009). *Cognitive and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') in combination with alcohol or cannabis in humans*. Radboud University Nijmegen, Nijmegen, the Netherlands.

- Netherlands.
21. Pijnacker, J. (2010). *Defeasible inference in autism: A behavioral and electrophysiological approach*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 22. De Vrijer, M. (2010). *Multisensory integration in spatial orientation*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 23. Vergeer, M. (2010). *Perceptual visibility and appearance: Effects of color and form*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 24. Levy, J. (2010). *In cerebro unveiling unconscious mechanisms during reading*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 25. Treder, M. S. (2010). *Symmetry in (inter)action*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 26. Horlings C.G.C. (2010). *A weak balance: Balance and falls in patients with neuromuscular disorders*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 27. Snaphaan, L.J.A.E. (2010). *Epidemiology of post-stroke behavioural consequences*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 28. Dado – Van Beek, H.E.A. (2010). *The regulation of cerebral perfusion in patients with Alzheimer's disease*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 29. Derks, N.M. (2010). *The role of the non-preganglionic Edinger-Westphal nucleus in sex-dependent stress adaptation in rodents*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 30. Wyczesany, M. (2010). *Covariation of mood and brain activity. Integration of subjective self-report data with quantitative EEG measures*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 31. Beurze S.M. (2010). *Cortical mechanisms for reach planning*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 32. Van Dijk, J.P. (2010). *On the Number of Motor Units*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 33. Lapatki, B.G. (2010). *The Facial Musculature - Characterization at a Motor Unit Level*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 34. Kok, P. (2010). *Word order and verb inflection in agrammatic sentence production*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 35. van Elk, M. (2010). *Action semantics: Functional and neural dynamics*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 36. Majdandzic, J. (2010). *Cerebral mechanisms of processing action goals in self and others*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 37. Snijders, T.M. (2010). *More than words - Neural and genetic dynamics of syntactic unification*. Radboud University Nijmegen, Nijmegen, the Netherlands.
 38. Grootens, K.P. (2010). *Cognitive dysfunction and effects of antipsychotics in schizophrenia and borderline personality disorder*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 39. Nieuwenhuis, I.L.C. (2010). *Memory consolidation: A process of integration – Converging evidence from MEG, fMRI and behavior*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

40. Menenti, L.M.E. (2010). *The right language: Differential hemispheric contributions to language production and comprehension in context*. Radboud University Nijmegen, Nijmegen, the Netherlands.
41. Van Dijk, H.P. (2010). *The state of the brain, how alpha oscillations shape behaviour and event related responses*. Radboud University Nijmegen, Nijmegen, the Netherlands.
42. Meulenbroek, O.V. (2010). *Neural correlates of episodic memory in healthy aging and Alzheimer's disease*. Radboud University Nijmegen, Nijmegen, the Netherlands.
43. Oude Nijhuis, L.B. (2010). *Modulation of human balance reactions*. Radboud University Nijmegen, Nijmegen, the Netherlands.
44. Qin, S. (2010). *Adaptive memory: Imaging medial temporal and prefrontal memory systems*. Radboud University Nijmegen, Nijmegen, the Netherlands.
45. Timmer, N.M. (2011). *The interaction of heparan sulfate proteoglycans with the amyloid protein*. Radboud University Nijmegen, Nijmegen, the Netherlands.
46. Crajé, C. (2011). *(A)typical motor planning and motor imagery*. Radboud University Nijmegen, Nijmegen, the Netherlands.
47. Van Grootel, T.J. (2011). *On the role of eye and head position in spatial localisation behaviour*. Radboud University Nijmegen, Nijmegen, the Netherlands.
48. Lamers, M.J.M. (2011). *Levels of selective attention in action planning*. Radboud University Nijmegen, Nijmegen, the Netherlands.
49. Van der Werf, J. (2011). *Cortical oscillatory activity in human visuomotor integration*. Radboud University Nijmegen, Nijmegen, the Netherlands.
50. Scheeringa, R. (2011). *On the relation between oscillatory EEG activity and the BOLD signal*. Radboud University Nijmegen, Nijmegen, the Netherlands.
51. Bögels, S. (2011). *The role of prosody in language comprehension: When prosodic breaks and pitch accents come into play*. Radboud University Nijmegen, Nijmegen, the Netherlands.
52. Ossewaarde, L. (2011). *The mood cycle: Hormonal influences on the female brain*. Radboud University Nijmegen, Nijmegen, the Netherlands.
53. Kuribara, M. (2011). *Environment-induced activation and growth of pituitary melanotrope cells of *Xenopus laevis**. Radboud University Nijmegen, Nijmegen, the Netherlands.
54. Helmich, R.C.G. (2011). *Cerebral reorganization in Parkinson's disease*. Radboud University Nijmegen, Nijmegen, the Netherlands.
55. Boelen, D. (2011). *Order out of chaos? Assessment and treatment of executive disorders in brain-injured patients*. Radboud University Nijmegen, Nijmegen, the Netherlands.
56. Koopmans, P.J. (2011). *fMRI of cortical layers*. Radboud University Nijmegen, Nijmegen, the Netherlands.
57. van der Linden, M.H. (2011). *Experience-based cortical plasticity in object category representation*. Radboud University Nijmegen, Nijmegen, the Netherlands.
58. Kleine, B.U. (2011). *Motor unit discharges - Physiological and diagnostic studies in ALS*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
59. Paulus, M. (2011). *Development of action perception: Neurocognitive mechanisms underlying children's processing of others' actions*. Radboud University Nijmegen, Nijmegen, the Netherlands.

60. Tieleman, A.A. (2011). *Myotonic dystrophy type 2. A newly diagnosed disease in the Netherlands*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
61. Van Leeuwen, T.M. (2011). *'How one can see what is not there': Neural mechanisms of grapheme-colour synaesthesia*. Radboud University Nijmegen, Nijmegen, the Netherlands.
62. Van Tilborg, I.A.D.A. (2011). *Procedural learning in cognitively impaired patients and its application in clinical practice*. Radboud University Nijmegen, Nijmegen, the Netherlands.
63. Bruinsma, I.B. (2011). *Amyloidogenic proteins in Alzheimer's disease and Parkinson's disease: Interaction with chaperones and inflammation*. Radboud University Nijmegen, Nijmegen, the Netherlands.
64. Voermans, N. (2011). *Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome; expanding the phenotype of inherited connective tissue disorders and investigating the role of the extracellular matrix in muscle*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
65. Reelick, M. (2011). *One step at a time. Disentangling the complexity of preventing falls in frail older persons*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
66. Buur, P.F. (2011). *Imaging in motion. Applications of multi-echo fMRI*. Radboud University Nijmegen, Nijmegen, the Netherlands.
67. Schaefer, R.S. (2011). *Measuring the mind's ear: EEG of music imagery*. Radboud University Nijmegen, Nijmegen, the Netherlands.
68. Xu, L. (2011). *The non-preganglionic Edinger-Westphal nucleus: An integration center for energy balance and stress adaptation*. Radboud University Nijmegen, Nijmegen, the Netherlands.
69. Schellekens, A.F.A. (2011). *Gene-environment interaction and intermediate phenotypes in alcohol dependence*. Radboud University Nijmegen, Nijmegen, the Netherlands.
70. Van Marle, H.J.F. (2011). *The amygdala on alert: A neuroimaging investigation into amygdala function during acute stress and its aftermath*. Radboud University Nijmegen, Nijmegen, the Netherlands.
71. De Laat, K.F. (2011). *Motor performance in individuals with cerebral small vessel disease: An MRI study*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
72. Mädebach, A. (2011). *Lexical access in speaking: Studies on lexical selection and cascading activation*. Radboud University Nijmegen, Nijmegen, the Netherlands.
73. Poelmans, G.J.V. (2011). *Genes and protein networks for neurodevelopmental disorders*. Radboud University Nijmegen, Nijmegen, the Netherlands.
74. Van Norden, A.G.W. (2011). *Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
75. Jansen, E.J.R. (2011). *New insights into V-ATPase functioning: the role of its accessory subunit Ac45 and a novel brain-specific Ac45 paralog*. Radboud University Nijmegen, Nijmegen, the Netherlands.

76. Haaxma, C.A. (2011). *New perspectives on preclinical and early stage Parkinson's disease*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
77. Haegens, S. (2012). *On the functional role of oscillatory neuronal activity in the somatosensory system*. Radboud University Nijmegen, Nijmegen, the Netherlands.
78. van Barneveld, D.C.P.B.M. (2012). *Integration of exteroceptive and interoceptive cues in spatial localization*. Radboud University Nijmegen, Nijmegen, the Netherlands.
79. Spies, P.E. (2012). *The reflection of Alzheimer disease in CSF*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
80. Helle, M. (2012). *Artery-specific perfusion measurements in the cerebral vasculature by magnetic resonance imaging*. Radboud University Nijmegen, Nijmegen, the Netherlands.
81. Egetemeir, J. (2012). *Neural correlates of real-life joint action*. Radboud University Nijmegen, Nijmegen, the Netherlands.
82. Janssen, L. (2012). *Planning and execution of (bi)manual grasping*. Radboud University Nijmegen, Nijmegen, the Netherlands.
83. Vermeer, S. (2012). *Clinical and genetic characterisation of autosomal recessive cerebellar ataxias*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
84. Vrins, S. (2012). *Shaping object boundaries: Contextual effects in infants and adults*. Radboud University Nijmegen, Nijmegen, the Netherlands.
85. Weber, K.M. (2012). *The language learning brain: Evidence from second language and bilingual studies of syntactic processing*. Radboud University Nijmegen, Nijmegen, the Netherlands.
86. Verhagen, L. (2012). *How to grasp a ripe tomato*. Utrecht University, Utrecht, the Netherlands.
87. Nonkes, L.J.P. (2012). *Serotonin transporter gene variance causes individual differences in rat behaviour: For better and for worse*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
88. Joosten-Weyn Banningh, L.W.A. (2012). *Learning to live with Mild Cognitive Impairment: development and evaluation of a psychological intervention for patients with Mild Cognitive Impairment and their significant others*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
89. Xiang, H.D. (2012). *The language networks of the brain*. Radboud University Nijmegen, Nijmegen, the Netherlands.
90. Snijders, A.H. (2012). *Tackling freezing of gait in Parkinson's disease*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
91. Rouwette, T.P.H. (2012). *Neuropathic pain and the brain - Differential involvement of corticotropin-releasing factor and urocortin 1 in acute and chronic pain processing*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
92. Van de Meerendonk, N. (2012). *States of indecision in the brain: Electrophysiological and hemodynamic reflections of monitoring in visual language perception*. Radboud University Nijmegen, Nijmegen, the Netherlands.
93. Sterrenburg, A. (2012). *The stress response of forebrain and midbrain regions: Neuropeptides, sex-specificity and epigenetics*. Radboud University Nijmegen,

- Nijmegen, The Netherlands.
94. Uithol, S. (2012). *Representing action and intention*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 95. Van Dam, W.O. (2012). *On the specificity and flexibility of embodied lexical-semantic representations*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 96. Slats, D. (2012). *CSF biomarkers of Alzheimer's disease: Serial sampling analysis and the study of circadian rhythmicity*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 97. Van Nuenen, B.F.L. (2012). *Cerebral reorganization in premotor parkinsonism*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 98. van Schouwenburg, M.R. (2012). *Fronto-striatal mechanisms of attentional control*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 99. Azar, M.G. (2012). *On the theory of reinforcement learning: Methods, convergence analysis and sample complexity*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 100. Meeuwissen, E.B. (2012). *Cortical oscillatory activity during memory formation*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 101. Arnold, J.F. (2012). *When mood meets memory: Neural and behavioral perspectives on emotional memory in health and depression*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 102. Gons, R.A.R. (2012). *Vascular risk factors in cerebral small vessel disease: A diffusion tensor imaging study*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 103. Wingbermühle, E. (2012). *Cognition and emotion in adults with Noonan syndrome: A neuropsychological perspective*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 104. Walentowska, W. (2012). *Facing emotional faces. The nature of automaticity of facial emotion processing studied with ERPs*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 105. Hoogman, M. (2012). *Imaging the effects of ADHD risk genes*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 106. Trammer, J. J. (2012). *Feedforward and feedback mechanisms in sensory motor control*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 107. Van Eijndhoven, P. (2012). *State and trait characteristics of early course major depressive disorder*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
 108. Visser, E. (2012). *Leaves and forests: Low level sound processing and methods for the large-scale analysis of white matter structure in autism*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 109. Van Tooren-Hoogenboom, N. (2012). *Neuronal communication in the synchronized brain. Investigating the functional role of visually-induced gamma band activity: Lessons from MEG*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 110. Henckens, M.J.A.G. (2012). *Imaging the stressed brain. Elucidating the time- and region-specific effects of stress hormones on brain function: A translational approach*.

Radboud University Nijmegen, Nijmegen, The Netherlands.

111. Van Kesteren, M.T.R. (2012). *Schemas in the brain: Influences of prior knowledge on learning, memory, and education*. Radboud University Nijmegen, Nijmegen, The Netherlands.
112. Brenders, P. (2012). *Cross-language interactions in beginning second language learners*. Radboud University Nijmegen, Nijmegen, The Netherlands.
113. Ter Horst, A.C. (2012). *Modulating motor imagery. Contextual, spatial and kinaesthetic influences*. Radboud University Nijmegen, Nijmegen, The Netherlands.
114. Tesink, C.M.J.Y. (2013). *Neurobiological insights into language comprehension in autism: Context matters*. Radboud University Nijmegen, Nijmegen, The Netherlands.
115. Böckler, A. (2013). *Looking at the world together. How others' attentional relations to jointly attended scenes shape cognitive processing*. Radboud University Nijmegen, Nijmegen, The Netherlands.
116. Van Dongen, E.V. (2013). *Sleeping to Remember. On the neural and behavioral mechanisms of sleep-dependent memory consolidation*. Radboud University Nijmegen, Nijmegen, The Netherlands.
117. Volman, I. (2013). *The neural and endocrine regulation of emotional actions*. Radboud University Nijmegen, Nijmegen, The Netherlands.
118. Buchholz, V. (2013). *Oscillatory activity in tactile remapping*. Radboud University Nijmegen, Nijmegen, The Netherlands.
119. Van Deurzen, P.A.M. (2013). *Information processing and depressive symptoms in healthy adolescents*. Radboud University Nijmegen, Nijmegen, The Netherlands.
120. Whitmarsh, S. (2013). *Nonreactivity and metacognition in mindfulness*. Radboud University Nijmegen, Nijmegen, The Netherlands.
121. Vesper, C. (2013). *Acting together: Mechanisms of intentional coordination*. Radboud University Nijmegen, Nijmegen, The Netherlands.
122. Lagro, J. (2013). *Cardiovascular and cerebrovascular physiological measurements in clinical practice and prognostics in geriatric patients*. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
123. Eskenazi, T.T. (2013). *You, us & them: From motor simulation to ascribed shared intentionality in social perception*. Radboud University Nijmegen, Nijmegen, The Netherlands.
124. Ondobaka, S. (2013). *On the conceptual and perceptual processing of own and others' behavior*. Radboud University Nijmegen, Nijmegen, The Netherlands.
125. Overvelde, J.A.A.M. (2013). *Which practice makes perfect? Experimental studies on the acquisition of movement sequences to identify the best learning condition in good and poor writers*. Radboud University Nijmegen, Nijmegen, The Netherlands.
126. Kalisvaart, J.P. (2013). *Visual ambiguity in perception and action*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
127. Kroes, M. (2013). *Altering memories for emotional experiences*. Radboud University Nijmegen, Nijmegen, The Netherlands.
128. Duijnhouwer, J. (2013). *Studies on the rotation problem in self-motion perception*. Radboud University Nijmegen, Nijmegen, The Netherlands.
129. Nijhuis, E.H.J (2013). *Macroscopic networks in the human brain: Mapping connectivity*

- in healthy and damaged brains*. University of Twente, Enschede, The Netherlands
130. Braakman, M. H. (2013). *Posttraumatic stress disorder with secondary psychotic features. A diagnostic validity study among refugees in the Netherlands*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 131. Zedlitz, A.M.E.E. (2013). *Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 132. Schoon, Y. (2013). *From a gait and falls clinic visit towards self-management of falls in frail elderly*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
 133. Jansen, D. (2013). *The role of nutrition in Alzheimer's disease - A study in transgenic mouse models for Alzheimer's disease and vascular disorders*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 134. Kos, M. (2013). *On the waves of language - Electrophysiological reflections on semantic and syntactic processing*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 135. Severens, M. (2013). *Towards clinical BCI applications: Assistive technology and gait rehabilitation*. Radboud University Nijmegen, Nijmegen, Sint Maartenskliniek, Nijmegen, The Netherlands.
 136. Bergmann, H. (2014). *Two is not always better than one: On the functional and neural (in)dependence of working memory and long-term memory*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 137. Wronka, E. (2013). *Searching for the biological basis of human mental abilities. The relationship between attention and intelligence studied with P3*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 138. Lüttjohann, A.K. (2013). *The role of the cortico-thalamo-cortical system in absence epilepsy*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 139. Brazil, I.A. (2013). *Change doesn't come easy: Dynamics of adaptive behavior in psychopathy*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 140. Zerbi, V. (2013). *Impact of nutrition on brain structure and function. A magnetic resonance imaging approach in Alzheimer mouse models*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 141. Delnooz, C.C.S. (2014). *Unravelling primary focal dystonia. A treatment update and new pathophysiological insights*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
 142. Bultena, S.S. (2013). *Bilingual processing of cognates and language switches in sentence context*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 143. Janssen, G. (2014). *Diagnostic assessment of psychiatric patients: A contextual perspective on executive functioning*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 144. Piai, V. Magalhães (2014). *Choosing our words: Lexical competition and the involvement of attention in spoken word production*. Radboud University Nijmegen, Nijmegen, The Netherlands.
 145. Van Ede, F. (2014). *Preparing for perception. On the attentional modulation, perceptual relevance and physiology of oscillatory neural activity*. Radboud University Nijmegen, Nijmegen, The Netherlands.

146. Brandmeyer, A. (2014). *Auditory perceptual learning via decoded EEG neurofeedback: a novel paradigm*. Radboud University Nijmegen, Nijmegen, The Netherlands.
147. Radke, S. (2014). *Acting social: Neuroendocrine and clinical modulations of approach and decision behavior*. Radboud University Nijmegen, Nijmegen, The Netherlands.
148. Simanova, I. (2014). *In search of conceptual representations in the brain: towards mind-reading*. Radboud University Nijmegen, Nijmegen, The Netherlands.
149. Kok, P. (2014). *On the role of expectation in visual perception: A top-down view of early visual cortex*. Radboud University Nijmegen, Nijmegen, The Netherlands.
150. Van Geldorp, B. (2014). *The long and the short of memory: Neuropsychological studies on the interaction of working memory and long-term memory formation*. Radboud University Nijmegen, Nijmegen, The Netherlands.
151. Meyer, M. (2014). *The developing brain in action - Individual and joint action processing*. Radboud University Nijmegen, Nijmegen, The Netherlands.
152. Wester, A. (2014). *Assessment of everyday memory in patients with alcohol-related cognitive disorders using the Rivermead Behavioural Memory Test*. Radboud University Nijmegen, Nijmegen, The Netherlands.
153. Koenraadt, K. (2014). *Shedding light on cortical control of movement*. Radboud University Nijmegen, Nijmegen; Sint Maartenskliniek, Nijmegen, The Netherlands.
154. Rutten-Jacobs, L.C.A. (2014). *Long-term prognosis after stroke in young adults*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
155. Herbert, M. (2014). *Facing uncertain diagnosis: the use of CSF biomarkers for the differential diagnosis of neurodegenerative diseases*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
156. Llera Arenas, A. (2014). *Adapting brain computer interfaces for non-stationary changes*. Radboud University Nijmegen, Nijmegen, The Netherlands.
157. Smulders, K. (2014). *Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Dissertations of the Parkinson Centre Nijmegen

1. Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, 17 June 2008
2. Maaïke Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, 27 May 2009
3. W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, 7 October 2009
4. Corinne G.C. Horlings. A weak balance: balance and falls in patients with neuromuscular disorders. Radboud University Nijmegen, 1 April 2010
5. Samyra H.J. Keus. Physiotherapy in Parkinson's disease: towards evidence-based practice. Leiden University, 29 April 2010
6. Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, 29 November 2010
7. Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, 29 November 2010
8. Rick C.G. Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, 24 May 2011
9. Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011
10. Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, 30 November 2011
11. Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, 6 December 2011
12. Johanna G. Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, 22 December 2011
13. Anke H. Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen, 4 June 2012
14. Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, 22 November 2012
15. Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, 10 December 2012
16. Wandana Nanhoe-Mahabier. Freezing and falling in Parkinson's disease: from the laboratory to the clinic. Radboud University Nijmegen, 13 February 2012
17. Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 6 March 2013
18. Arlène D. Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, 6 March 2013
19. Tjitske Boonstra. The Contribution of each leg to bipedal balance control. University Twente, 6 June 2013
20. Catherine C.S. Delnooz. Unravelling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, 7 January 2014
21. Marjolein A. Van der Marck. The many faces of Parkinson's disease: towards a

multifaceted approach? Radboud University Nijmegen, 10 January 2014

22. Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, 21 May 2014

