VIRTUAL VISUAL CUES: VICE OR VIRTUE?

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

"On a bit of a windy day, I was waiting at the bus stop. I felt nervous whether I would make it this time. The bus approached at high speed, trying to catch up with its schedule. I wanted to walk towards the bus. But I didn't. I couldn't. My feet felt as if they were glued to the floor and I couldn't get them to begin stepping forward. The bus stopped. My anxiety rose, the bus would not wait for too long. My feet were still stuck, unwilling to take me forward. I raised my hand, and asked the driver to wait for me. But the wind took my mumbled words, and the bus driver misunderstood my hand gesture. He kindly smiled at me, waived back, closed the door, and drove away. Without me." – Personal experience shared by a person with Parkinson's disease during one of the experiments in the current thesis.

Freezing of gait

This anecdote painfully illustrates how bothersome freezing of gait (FOG) in persons with Parkinson's disease (PD) can be (Box 1). FOG is operationally defined as a 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' (6), often described by patients as the feeling as if their feet are suddenly being 'glued' to the floor. Such an abrupt 'freezing' of the feet, while the upper body is continuing on its forward moving track, increases the risks of falling, fall-related injuries, and fear of falling (7). FOG impedes a person's independence in daily life activities, and negatively impacts the quality of life (8).

Epidemiology

FOG is not restricted to PD, and can also occur in a range of other extrapyramidal movement disorders, such as progressive supranuclear palsy, multiple system atrophy, or vascular parkinsonism (7). Over 60% of persons with PD ultimately develop FOG during the course of their disease, usually at later disease stages (9). FOG is more likely to occur in those patients with the 'postural instability gait disorder' (PIGD) subtype of PD (Box 1), and in patients with cognitive executive dysfunction (10-14), depression (15), or anxiety (15).

Clinical manifestations

Known FOG-provoking triggers include turning (particularly narrow turns in tight quarters), gait initiation, and passing through narrow passages such as

doorways. However, especially in advanced disease stages, FOG might also occur during walking straight in an open space (2, 6, 16). Additionally, emotional distress, cognitive dual tasks, and experiencing time pressure (such as in the anecdote described above) predispose to FOG development (4, 5, 17). Three distinct clinical subtypes of FOG can be distinguished: 1) trembling in place, with a tremor of the legs but no effective forward stepping; 2) shuffling forward with short steps; and 3) akinesia, with a complete absence of leg movement (5, 6). The first two phenotypes are by far the most common, and the a-kinetic type usually only occurs when affected persons are in a profound OFF state. Although FOG is by definition a paroxysmal phenomenon, persons with PD and FOG also exhibit continuously present gait abnormalities in between FOG episodes. A lower gait velocity (18), shorter stride length (18), higher cadence (18), and higher stride length variability (19) are reflections of problems in the scaling, timing and coordination of stepping in persons with PD and FOG compared to those without FOG.

Box 1. Parkinson's disease

Parkinson's disease (PD) was first described in 1817 by James Parkinson in his essay on the "Shaking Palsy". With an estimated prevalence between 108 – 257 per 100 000 persons (20), and an incidence ranging from 11 – 19 per 100.000 person-years (20), PD is the most common neurodegenerative disorder after Alzheimer's disease (21). The prevalence (22) and incidence of PD increase nearly exponentially with age (23). Considering the global population aging, and because of environmental factors such as pollution, a sharp rise in the number of persons with PD is foreseen (24).

The primary pathological hallmark of PD is early degeneration of dopaminergic neurons in the substantia nigra pars compacta, as well as in other brain regions such as the nucleus basalis of Meynert, pedunculopontine nucleus, raphe nucleus, hypothalamus, amygdala, and dorsal motor nucleus of the vagal nerve (21). A second pathological feature of PD is the aggregation of misfolded α-synuclein (contained

within Lewy bodies) in the brain, spinal cord, and peripheral nervous system (21).

PD is characterized by a wide range of motor and non-motor symptoms. The classical motor symptoms include bradykinesia, muscular rigidity, a 4-6 Hz rest tremor, postural instability, and gait impairment. Based on these motor symptoms, two major subtypes of PD can be distinguished: tremor-dominant ('TD-PD'), and predominantly postural instability gait disorder ('PIGD-PD'). This dichotomy does not represent the richly varied symptomatology of PD well. Therefore, research groups worldwide are now trying to build more fine-grained personal disease profiles (25). Non-motor symptoms in PD include autonomic dysfunction, sleep disturbances, cognitive impairment, and psychiatric symptoms (21).

Despite considerable research efforts, a disease-modifying or curative treatment for PD is not yet available. Current symptomatic therapies encompass pharmacotherapy aimed at enhancing cerebral dopaminergic transmission, surgical therapies such as deep brain stimulation, and neurorehabilitation applying a multidisciplinary team approach including physiotherapy, occupational therapy, speech therapy, specialized nurses, and many other professional disciplines (26, 27).

Pathophysiology

The pathophysiology of FOG is complex and involves one or, more likely, multiple lesions in a complex gait circuitry (1-5). FOG is thought to arise from an over-activation of inhibitory projections from the basal ganglia to the thalamus and locomotor regions in the brainstem that are involved in coordinating gait (1) (Figure 1 & 2). In turn, the inhibitory output of the basal ganglia is under control of the cerebral cortex, thalamus, and cerebellum. Any functional disruption in the neural control of these structures over the basal ganglia, can lead to FOG. Therefore, the origin of FOG is likely to differ across patients. This heterogeneous pathophysiology of FOG might very well explain the various FOG subtypes and the variety in FOG triggers recognized amongst patients (1).

Treatment

In most patients, FOG occurs exclusively or worsens when dopaminergic medication wears off. Therefore, the pharmacological treatment of FOG is mainly aimed at keeping dopaminergic levels sufficiently high. However, FOG often persists at least to some extent, and in some patients does not improve at all, even under optimized pharmacotherapy (28). In fact, although rare, dopaminergic medication may sometimes induce FOG which occurs exclusively during the ON state (29). An arresting observation is that FOG only occurs in persons on levodopa treatment, and not in persons with untreated PD, even in advanced disease stages (30-32). This raises a paradox of levodopa being related to the emergence of FOG on the one hand, and reducing FOG once the phenomenon has developed on the other hand (30). One hypothesis is that the long-term pulsatile administration of levodopa alters synapse plasticity in especially dopaminergic motor loops, leading to higher stimulation thresholds within the motor circuitry (30). If this hypothesis is confirmed, a logical next question would be whether continuous rather than pulsatile levodopa treatment would be favourable with regard to the development of FOG (30).

Deep brain stimulation (DBS) of the subthalamic nucleus can reduce all three subtypes of FOG in patients that are responsive to dopaminergic medication, although the long-term effects remain to be established (33-36). Whether the pedunculopontine nucleus constitutes an appropriate DBS target to treat FOG is under investigation, but does not seem the panacea in treating FOG (35). Neurorehabilitation, such as attentional and cueing strategies, comprises an integral part of the treatment of FOG (37-39). Attentional strategies include paying attention to every step, and consciously taking larger steps, shifting body weight or lifting the legs higher (40, 41). Cueing strategies are discussed in more detail in the next paragraph.
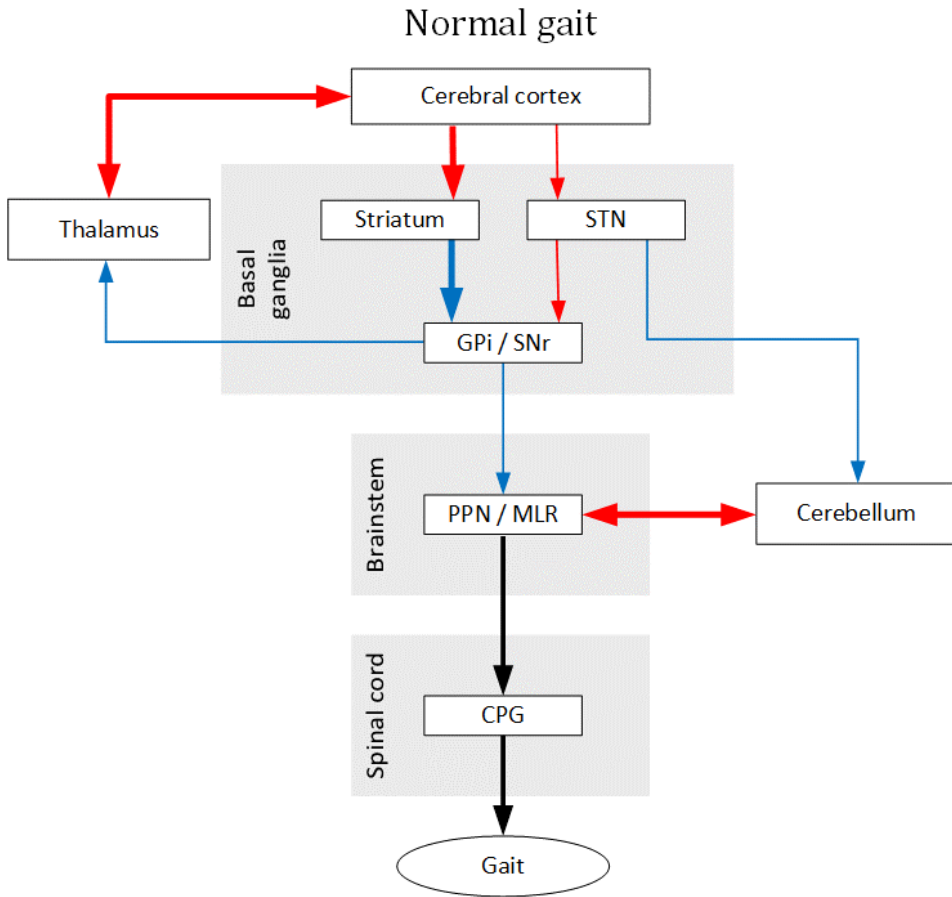
Figure 1. Schematic representation of structures and networks involved in normal gait. During walking, areas in the cerebral cortex involved in motor planning activate the striatum, and to a lesser extent the subthalamic nucleus (STN). The predominance of the striatal over the STN activation leads to an inhibition of the globus pallidus pars interna (GPi) and substantia nigra pars reticulate (SNr), releasing the inhibition of the pedunculopontine nucleus (PPN) and mesencephalic locomotor regions (MLR) in the brainstem. The PPN / MLR integrate input from the corticostrial and corticothalamic systems on motor planning, and from the cerebellovestibular balance system on sensory stimuli, to select the appropriate motor plan. These motor plans are outputted to the central pattern generators (CPG) in the spinal cord, resulting in normal gait. Blue arrow = inhibitory; Red arrow = excitatory. The arrow thickness represents the size of the output. (1-5).
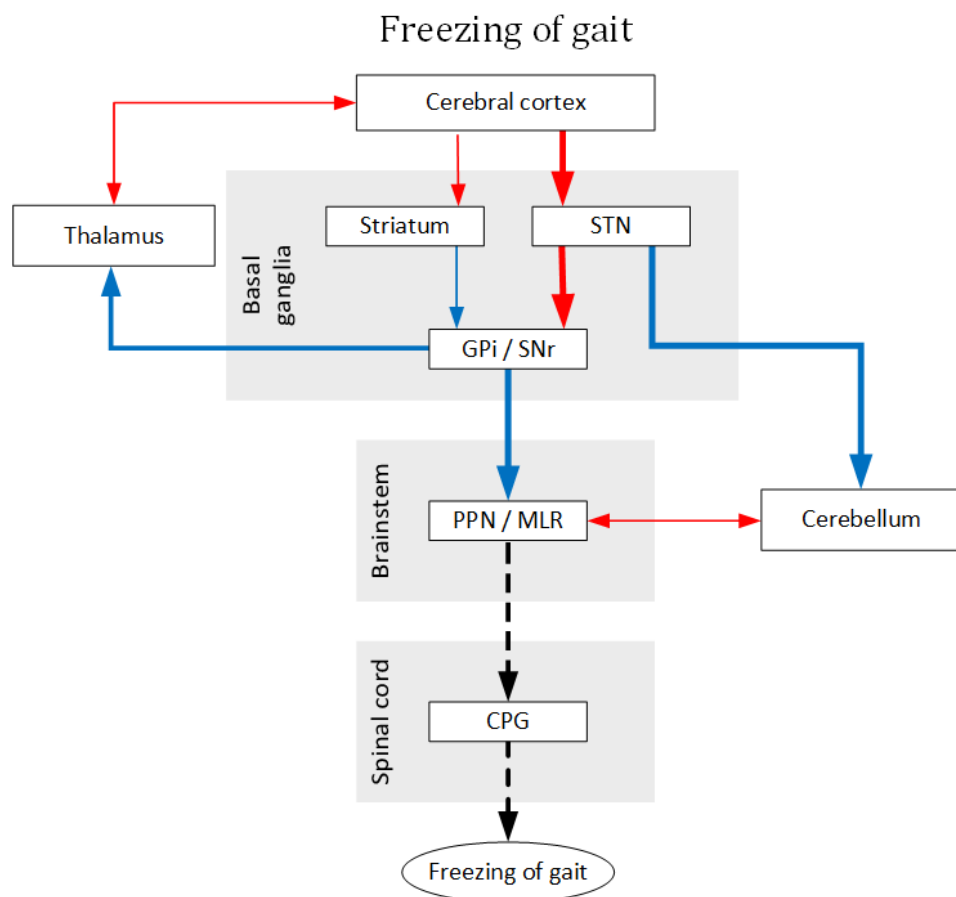
Figure 2. Schematic representation of structures and networks involved in freezing of gait (FOG). Core to the development of FOG is an excessive inhibitory output from the globus pallidus pars interna (GPi) / substantia nigra pars reticulate (SNr) in the basal ganglia to the pedunculopontine nucleus (PPN) / mesencephalic locomotor region (MLR) in the brainstem, disrupting the selection and output of the appropriate motor programs for walking. Any derangement in corticothalamic, corticostriatal, or cerebellovestibular networks that results in this overinhibition of GPi / SNr could potentially lead to FOG.

CPG, central pattern generators; STN, subthalamic nucleus. Blue arrow = inhibitory output; Red arrow = excitatory output. The thickness of the arrows represents the size of the output. (1-5)

Cueing

Definition of cueing

Cueing is defined as the application of spatial or temporal stimuli to facilitate gait initiation and continuation (37, 38, 42). Cues can be either internally (e.g. mentally counting) or externally generated. External cues can be auditory (e.g. a metronome), visual (e.g. transverse bars on the floor) or haptic (e.g. vibrating wrist bands or – more recently – vibrating socks (43)). Although cues are often rhythmic, such as the beat of a metronome or a series of stripes pasted onto the floor, a single cue, for example a mark on the floor as a target to walk towards, can also serve to improve gait.

Effects of cueing

Cueing encompasses an effective strategy to reduce the occurrence and duration of FOG, and to stabilize the gait pattern in persons with PD and FOG (42, 44-46). However, patients strongly vary in their response to different cueing strategies and modalities (42, 45). There exists no 'one size fits all'-cueing strategy, and considering the heterogeneous pathophysiology of FOG, it is highly unlikely there will ever be one. Which cueing strategy is of most benefit to an individual patient cannot yet be predicted, and its selection currently relies on trial-and-error. Attempts to develop more personalized cueing and other rehabilitation strategies are underway (27, 41).

Mechanisms underlying cueing

The hypothesized mechanisms underlying the effects of cues are multifold and most likely non-exclusive. First, cues are thought to redirect automatized behaviour (which relies on affected basal ganglia circuitries) towards goal-directed behaviour (which is relatively spared) (47). Second, cues might redirect attention towards gait, thereby reducing the interference of concurrent motor, cognitive or affective processes (48). Third, visual cues in particular are thought to aid in the scaling of movement (44), helping to overcome the inability to produce and maintain a proper, stable step length that leads to FOG (18). Fourth, rhythmic cues (such as a metronome) provide an external rhythm to which motor timing can be synchronized, restoring the

motor timing dysrhythmia that patients with FOG exhibit if they are fully dependent upon their defective internal timing mechanism (49, 50).

Wearable cueing devices

With the goal of supporting patient mobility during everyday activities in their own living environment, cues must be ambulatory, rather than stationary, to be useful in daily life. This is relatively easy for auditory cues, which can be delivered via ear buds. However, especially visual cues are challenging to provide in a wearable fashion. Laser lines projected from a rolling walker (51-53) or walking cane (52, 54) can be effective in some, but not all, patients using a walking aid. Light flashes delivered via light-emitting diodes attached to regular glasses (44) or smart glasses (55) were disliked by most patients (44, 55). A laser line projected from the shoe tip gave promising results in a laboratory-based study (56) and a pilot study at home (57), and awaits confirmation in larger studies.

Visual cueing solutions which are clearly noticeable to bystanders can cause considerable stigma for persons with PD, thereby limiting their acceptance. Also, they can cause anxiety to the environment - one participant in a study investigating the ambulatory application of a laser line from the shoe tip (57) was dragged out of a public bus by the police because he was suspected to wear bomb shoes (58). This underscores the need for unobtrusive and inconspicuous cueing devices.

Despite the variety of cueing devices under investigation, a user-friendly, inconspicuous, wearable device providing visual cues tailored to personal preference and effectivity, is not yet available.

The recent technological development of smart glasses potentially provides a versatile platform to deliver wearable, personalized visual cues. A subtype of smart glasses, called augmented reality (AR) glasses, can display visual information, such as cues, on top of a user's visual field. The delivery of visual cues through augmented reality glasses is still at an early stage, with its first applications being promising (55, 59), but quickly outdated due to the rapid development of improved devices.

The question whether visual cues delivered through augmented reality glasses can improve FOG and gait in persons with PD, comprises the common red thread running through the current thesis.

Aim and outline of this thesis

This thesis aims to explore whether wearable visual cues delivered through augmented reality glasses improve FOG and gait in persons with PD. For this purpose, the thesis is subdivided into three parts.

Part I The position and prerequisites of cueing in neurorehabilitation in Parkinson's disease

Chapter 2 describes the position of neurorehabilitation in Parkinson's disease, with a special emphasis on wearable visual cueing strategies. **Chapter 3** discusses visual and ocular disorders which are prevalent in persons with PD. Obviously, applying visual cues in a person with poor eye sight is doomed to fail. Hence should visual disturbances be considered when developing visual cues.

Part II Novel cues aimed to alleviate freezing of gait

Chapter 4 reports a person with PD who discovered that he could relieve his FOG when gently pressing his fingertips onto his temples. The inventiveness of patients and caregivers in finding ways to overcome their FOG is further accentuated in **Chapter 5**, describing a person with PD and severe FOG who could still climb stairs, and who also responded remarkably well to the illusion of a three-dimensional staircase painted onto the floor, serving as a visual cue. **Chapter 6** investigates whether three-dimensional visual cues displayed through custom-made smart glasses can alleviate FOG and improve gait in persons with PD. **Chapter 7** describes a single person with PD, aiming to investigate whether the wearing of augmented reality glasses influenced FOG, and the effect this had on the potency of various cues. The visual cues in **Chapters 6 & 7** were aimed at supporting straight-path walking, even though most FOG episodes occur during making turns while standing or walking. For that reason, in **Chapter 8**, we investigate whether augmented reality visual cues delivered through an updated set of smart glasses can improve FOG during turning in place.

Part III Research paradigms to study cueing

In studies investigating FOG and cueing, it proves notoriously difficult to provoke FOG. The most prevalent FOG trigger, turning in place, cannot be

used when assessing FOG during straight path walking. Dual tasks constitute a valid alternative to trigger FOG. In **Chapter 9**, I validate the Auditory Stroop Task to increase cognitive load during walking tasks.

The neurophysiological pathways mediating the effects of visual cues are largely unknown. Unravelling these would enable a mechanism-based development of more effective, personalized, cueing strategies. This requires a research paradigm for neuroimaging and behavioural studies. In **Chapter 10**, I extend an established virtual environment paradigm by incorporating visual cues to study visual cueing in persons with PD and FOG.

Part IV Summary and discussion
Finally, in **Chapter 11**, I provide summaries in English and Dutch of the main findings in these various studies. The crosslink to existing research will be discussed, as well as venues for future work.

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PART I

THE POSITION AND PREREQUISITES OF CUEING IN NEUROREHABILITATION IN PARKINSON'S DISEASE

CHAPTER 2

NEUROREHABILITATION IN PARKINSON'S DISEASE

Abstract

Parkinson's disease is a common neurodegenerative disorder, resulting in both motor and non-motor symptoms that significantly reduce quality of life. Treatment consists of both pharmaceutical and non-pharmaceutical treatment approaches. Neurorehabilitation is an important non-pharmaceutical treatment approach, and a prime component of this is formed by the training of behavioural adaptations that can assist patients to cope better with their motor and non-motor symptoms. Optimal delivery of neurorehabilitation requires a tailor-made, personalized approach. In this review we discuss the great potential for growth in the field of neurorehabilitation. Specifically, we will focus on four relatively new developments: visual rehabilitation (because Parkinson patients are very dependent on optimal vision); cueing delivered by wearable devices (allowing for objective, continuous, and quantitative detection of mobility problems, such that cueing can be delivered effectively in an on-demand manner—ie, with external cues being delivered only at a time when they are needed most); exergaming (to promote compliance with exercise programs); and telemedicine (allowing for delivery of expert rehabilitation advice to the patient's own home). Evidence in these new fields is growing, based on good clinical trials, fuelling hope that state-of-the-art neurorehabilitation can make a real impact on improving the quality of life of patients affected by Parkinson's disease.

Introduction

Parkinson's disease (PD) is characterized by the progressive development of a wide array of motor and non-motor symptoms. The resultant disability can be alleviated only in part by pharmaceutical agents, which have only a limited effect on axial motor symptoms, and no effect on many non-motor symptoms. Moreover, pharmacotherapy is hampered by the progressive development of dose-limiting side-effects. Postural instability and freezing of gait (FOG) – brief episodes of inability to produce effective forward steps despite the intention to walk – are examples of common and disabling symptoms that respond insufficiently to medication. This commonly leads to falls, reduced mobility and diminished quality of life (1). Fortunately, evidence is growing that neurorehabilitation approaches can offer relief of such treatment-resistant symptoms and signs, by exploiting behavioural adaptations that bypass the defective motor circuitries.

Illustrative case

As an example we introduce an 82-year old man with PD who developed severe FOG. He had successfully used auditory cues to improve his FOG for several years, but over time he had started to notice that these cues began losing their effectiveness. Being a former engineer, he invented his own new cueing strategy, using various types of 3D visual cues that he incorporated in and around his house, with robust effects. This included e.g. wooden bars nailed to the floor, which forced him to consciously step over these obstacles. Surprisingly, these beneficial effects were totally absent when using 2D visual cues, such as pieces of white tape pasted onto the floor (2). This example underscores several messages: (a) the potential effectiveness of behavioural adaptations, as an important component of neurorehabilitation for patients with PD (3); (b) the creativity of patients in finding these solutions themselves; (c) the need for an individually tailored approach; and (d) the need to have a good vision (otherwise the visual cues would go by unnoticed).

Neurorehabilitation for Parkinson patients

Neurorehabilitation, including behavioural adaptations, can play an important role in the management of PD, by helping patients to deal with the

decline in functioning while optimizing participation and quality of life. Donaghy (4) defined neurorehabilitation as '*a process that aims to optimize a person's participation in society and sense of well-being*'. This broad definition highlights the scope of the domain of neurorehabilitation; it offers a wide range of therapies that are potentially helpful for many aspects of PD. The focus is on the patient as a person; the goals usually relate not only to disease symptoms, but also to social functioning and well-being (4). Compared to medical management (pharmacotherapy and, to a lesser extent, neurosurgery), neurorehabilitation has historically played a relatively modest role in the management of PD. However, this field has recently gone through major developments; the scientific evidence on its' effectiveness is increasing (5), and neurorehabilitation is increasingly being integrated in the multidisciplinary care pathways for patients with PD (6). Moreover, interesting new treatment modalities are arising, with positive initial experience in clinical studies. Many professional disciplines are involved in neurorehabilitation, including e.g. physiotherapists, occupational therapists and speech- language therapists; all these professionals need to integrate their own specific treatment contribution with each other, and align this with medical management (7). This review does not aim to review all aspects of neurorehabilitation in PD. Instead, we focus on several promising new perspectives (Figure 1). Specifically, we will first address an important, but easily overlooked requirement for effective neurorehabilitation: optimal visual functioning. Next, we will describe three relatively new emerging technological developments that can be integrated into neurorehabilitation: cueing via wearables, exergaming and telemedicine.
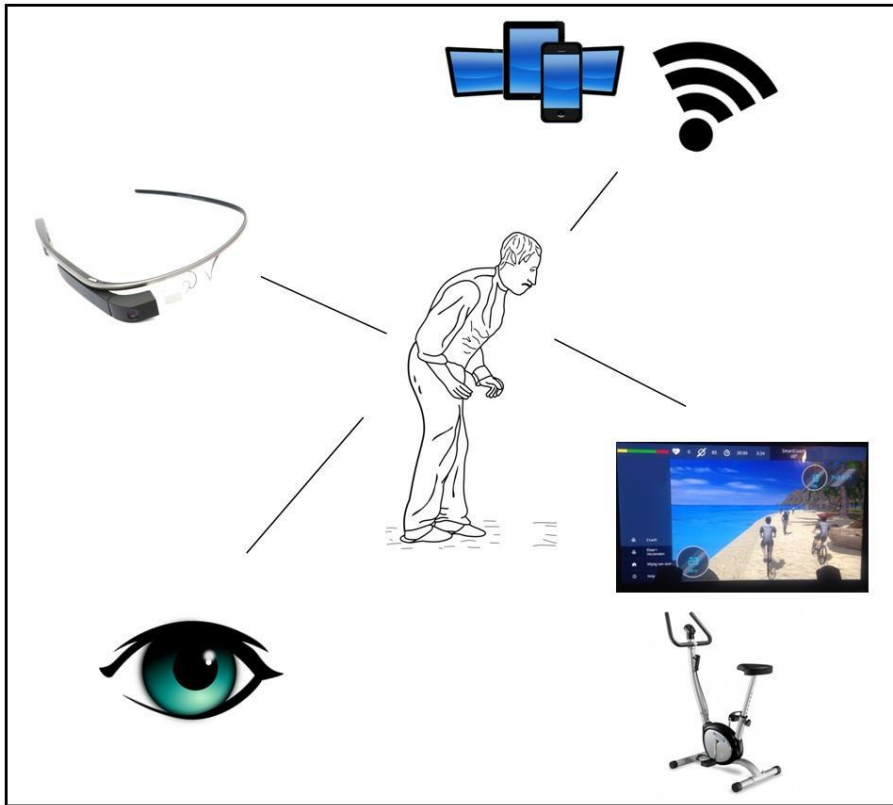
Figure 1. Overview of promising new treatment modalities that can contribute to optimal and personalized delivery of neurorehabilitation.

Visual impairment

Treatment of visual impairments is not traditionally part of neurorehabilitation. Ophthalmologic problems are, however, very common in PD (8). Optimal vision is an important requirement for mobility for any person, but in particular for patients with PD who are exceptionally dependent upon their vision to compensate for defects in their automatic motor behaviour, e.g. gait impairments (take visual cueing as an example). Screening for (and dedicated treatment of) visual impairment therefore deserves careful attention during neurorehabilitation. Indeed, ophthalmologic problems negatively affect walking, mobility, reading, driving, social participation, and quality of life (9). Moreover, PD patients with visual problems have higher fall

rates (10). Importantly, numerous visual problems can arise at many levels of the visual pathway in patients with PD. This includes e.g. dry eyes, ocular motor disturbances, impaired colour and contrast vision, and visual hallucinations (8, 11-13). Both clinicians and patients are mostly unaware of these visual impairments. Obviously, rehabilitation professionals are not equipped to diagnose or treat the whole gamut of visual impairments. However, screening for presence of gross visual or oculomotor abnormalities should always be part of the rehabilitation approach. Sometimes small adjustments can be recommended that may already make a huge difference. Prescription of base in prisms by an ophthalmologist or optometrist can, for example, help to overcome convergence insufficiency; enabling patients to see more depth, which helps them in daily life with walking the stairs and seeing for example 3D visual cues. Other problems are more complex and require treatment by an ophthalmologist. We therefore feel that close cooperation with an ophthalmologist is needed during neurorehabilitation in PD.

We will illustrate the potential effectiveness of screening for (and treatment of) visual impairments in neurorehabilitation by introducing three frequently occurring visual problems. First, PD patients often blink less frequently. This can cause dry eyes and, in turn, result in blurry vision, pain, a sandy/gritty feeling in the eyes and intermittent tearing. This is troublesome for patients, and visual acuity can be endangered due to the blurring. With a Schirmer's test, a brief test using a thin paper stroke that absorbs the tear fluid, it is possible to evaluate the amount of tear production of a patient. If dry eyes exist, artificial tears and explanation about blinking can reduce complaints and improve visual functioning, making it easier to see sharp and avoid pain and irritation (8, 9).

A second visual problem that limits both patients' mobility and safety is impaired contrast sensitivity and colour discrimination. This reduces the patient's ability to see in situations with low light, and makes driving, walking or cycling in darkness more dangerous. Non-invasive testing with specific charts and colour arranging tests can identify these problems. Special contrast enhancing glasses exist that improve these impairments and can be prescribed by an ophthalmologist or optometrist. Problems with reading in the dark, e.g.

on a computer, tablet or smartphone, can quite easily be improved by changing settings that enable patients to work with different coloured backgrounds and font types (8, 9).

Third, like mentioned before, PD patients often have convergence insufficiency and oculomotor troubles, so both eyes cannot fully cooperate to see depth and follow what a patient wants to see. This makes it difficult to read for example a newspaper or labels. Patients are sometimes unable to see the outer lines of the text they read. An ophthalmologist or optometrist can prescribe base-in prisms that can help to solve convergence insufficiency.

In summary, although visual impairments cannot necessarily be solved by neurorehabilitation, allied health professionals are important in screening for visual impairments that disable PD patients in daily life. Together with ophthalmologists, some visual problems can be solved or improved, making rehabilitation more effective. In addition, allied health professionals can practice with patients how to use visual assistive devices to improve functioning in daily life.

Cueing via wearables

External auditory, visual or tactile cues like a metronome beat or striped bars on the floor are established non-pharmaceutical methods to overcome gait difficulties by bypassing deficient activation of the basal ganglia/supplementary motor area circuit (13). Interestingly, improvements in gait and mobility – achieved in a cueing training program delivered at home – decreased considerably within weeks after discontinuing the training program (14), stressing the need for permanent cueing devices that provide external cues during, but not interfering with, daily life. Cues sometimes lose their effectiveness over time, as was illustrated by the case history in the Introduction. This might be overcome by only offering cues 'on demand' or by adjusting the nature of the cues when the effect is wearing off. Different cues appear to be effective in, and preferred by, different patients, underscoring the need for personalized care (14, 15). There is a need for portable, inconspicuous, user-friendly, cost efficient devices providing personalized cues 'on demand' in daily life situations. Such devices are currently being developed,

incorporating new technologies. Walking sticks (16, 17) and rolling walkers (18) projecting a laser line on the floor have shown efficacy in overcoming FOG and reducing falls in some, but not all patients (1, 16, 17). Light emitting diodes (LEDs) (15, 19) and an auditory device (20) incorporated in glasses are effective in improving gait parameters in laboratory settings, but the practical applicability in the home setting has not yet been established. Wearable 'mini computers' in the form of smart glasses can augment reality, overlaying pertinent information (like visual cues) on top of the users' visual field. These devices may respond to voice or gesture commands, but even more importantly, can potentially also respond to automatically sensed episodes of FOG or real-time object recognition, thereby offering cues at a time when they are needed most. The type, appearance and frequency of cues should be adapted to each patient's personal needs. Smart glasses can also support other neurorehabilitation applications, e.g. by supporting visually impaired patients through contrast-enhancing functions and magnification of view. In order to provide cues 'on demand', detection strategies are being developed which reliably detect (preferably early markers of) episodes of FOG (1). In a user requirements survey, PD patients responded enthusiastically to the idea of smart glasses and assistive technology to facilitate daily living activities. However, respondents were concerned about cost, appearance, efficacy and potential side effects. The next generation of devices for FOG detection and provision of cues should be developed together with patients and be tested thoroughly on efficacy, side effects and, cost-effectiveness. As such, these devices hold great promise for becoming personalized, patient-tailored neurorehabilitation assistants in PD.

Gaming

Gaming, e.g. the use of videogames and virtual reality, is a relatively new aspect of training, not only in PD, but also for other patient populations like stroke, dementia, or cancer (21). Gaming has a number of advantages compared to traditional neurorehabilitation: training can be aimed very specifically on e.g. balance, endurance or cognition, exercises are (or gradually become) more challenging, it is often perceived as enjoyable which increases long term adherence, a competitive element can be a motivating factor, and,

gaming can in many cases be performed in the home situation which increases the frequency of training (5, 21).

The two main goals of gaming include: gaming to promote compliance to another intervention, like exercise (this combination has been termed exergaming); or to offer a new treatment modality in its own right (e.g. gaming to enhance cognition and motor functioning).

Exergaming

Adding cognitive elements to physical training has recently been suggested to be beneficial for PD patients (22). Gaming usually requires physical and cognitive capacities and gaming may also result in both motor- and cognitive improvements. In addition to the previously mentioned advantages of gaming, incorporating goal-based training with aerobic exercise potentially also enhances experience-dependent neuroplasticity and may improve both cognitive and automatic components of motor control (22). Gaming is extremely suitable for adding cognitive elements to exercise. Games using for example virtual dancing and virtual bicycling (23) are examples of new interventions being studied (5, 24).

Gaming as a new treatment modality

Rehabilitation programs using gaming can also be primarily physical or cognitive in nature (5). Games are being used to offer gait and balance training, for example by virtual cues and obstacles on a treadmill (5, 23).

Other games are purely cognitive and do not require movements or physical capacities. A recent study compared a pure cognitive game on a computer with a motion-controlled sports game (Nintendo Wii sports) (25). Specifically, the cognitive training focused on multiple domains including attention, working memory and executive functioning. The results showed that both training approaches improved cognition equally, but the physical training afforded greater improvements in attention. Which is interesting because of the potential additional motor benefits of performing a physical game.

Gaming obviously also introduces several challenges. Safety is a major issue when advising a physical game in the home situation; this should be assessed

and supervised carefully by a professional. Also, the costs of gaming devices or equipment are a concern. Furthermore, games should be tailored specifically to the needs and capacities of PD patients. Taken together, the perceived benefits of gaming on both cognition and motor functioning warrant further exploration. Certainly, research in this field represents an exciting new domain of neurorehabilitation.

Telemedicine

Use of telecommunication technology to deliver care at a distance is a potentially cost-effective and efficient upcoming phenomenon that can be used in neurorehabilitation (26). Healthcare access is currently limited for many patients worldwide, for several reasons. Examples include understaffing and an uneven distribution of highly specialized clinicians. Also, disabled patients have difficulty travelling (long) distances to the clinic. Certainly for rehabilitation, many PD patients are required to visit an (outpatient) clinic regularly. Delivering care at a distance could offer a solution for the growing number of PD patients that need treatment by experts, and for a long period of time (26).

The advantages of using telemedicine are not just restricted to reducing travelling time. It also gives patients the opportunity to integrate training or practice into their daily life circumstances. Rehabilitation at a distance, like physiotherapy and speech therapy at home, can increase the maintenance of effect. Furthermore, gaming elements, as described above, can also be integrated into remote care. An excellent example is the treatment offered in an ongoing randomized controlled trial (23) where patients perform an aerobic exercise training at home. Training is performed on a stationary bicycle that is equipped with gaming elements; training intensity is adjusted automatically to the patients' heart rate. Progress is monitored from a distance by the research team, and is also made accessible to the patient on an iPad app. A personal coach (physiotherapist) can access the progress booked in each training session through an online application and has telephone contact with the patient every fortnight to adjust the training frequency or intensity when necessary.

Another emerging field is the remote monitoring of daily functioning using wearable sensors. For example, smartphone apps can be used to monitor symptoms (e.g. voice, gait, finger tapping) and behaviour (e.g. physical activity) longitudinally on a day-by-day basis (27). Gathering such data with a smartphone application seems feasible (27, 28), although the validity of the findings remains an issue. In the future, real-life information gathered by wearable sensors may be used by clinicians in making better informed management decisions.

Online or remote consultation of professionals has been explored using virtual house calls done by a PD specialist. This method proved to be feasible, both to patients and clinicians, while cost-effectiveness will be determined in an ongoing study (27, 29). Most patients would prefer to get a well-balanced combination of real life and telemedicine contact (28-30). In Canada (the Ontario Telemedicine Network) and the Netherlands (ParkinsonNet approach), advanced systems already use telemedicine successfully in daily practice (7, 26). Important limitations in implementing telemedicine include the limited reimbursement for remote care, the costs of high-quality telecommunication equipment and privacy issues considering data-transfer of patients. Ongoing technological advances, however, will offer ample opportunity to further utilize telemedicine in neurorehabilitation.

Discussion

We have described several emerging developments in the field of neurorehabilitation. We have highlighted the importance of good vision, as an essential requirement for optimal neurorehabilitation, and we have advocated the integration of ophthalmologists into the multidisciplinary treatment team in PD. A lot of work, however, remains to be done. The exact pathophysiological mechanisms underlying visual problems in PD remain unknown, and optimal screening and management protocols must be determined. Other work should identify the optimal behavioural adaptations that can be applied in rehabilitation to compensate for disturbed vision. Additionally, we have reviewed several promising technological advances that may support both patients and clinicians in their desire for delivery of more personalized care, tailored to actual needs as they are perceived in the home

situation. We discussed some interesting developments, including wearable cueing methods (like those provided by smart glasses), gaming techniques and telemedicine approaches.

The biggest challenge remains to gather robust scientific evidence on the (cost-) effectiveness of these new rehabilitation approaches. It has, for example, proved difficult to select appropriate outcome measures that are capable of measuring all clinically relevant changes in a heterogeneous population that received a tailor-made, personalized (and therefore also heterogeneous) intervention. The question is whether traditional study designs such as RCTs are the only way to gather the required evidence, or whether e.g. real-life observational studies in large and unselected populations (with long follow-up) might also create useful new insights. Finally, more works needs to determine the adequate "dosage" of neurorehabilitation. Pending these new studies, the good news for patients is that various exciting new developments are appearing on the horizon, and that the evidence-base for these novel interventions is growing (5), creating realistic perspectives for greater independence and less disability in the foreseeable future.

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CHAPTER 3

OCULAR AND VISUAL DISORDERS IN PARKINSON'S DISEASE

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Abstract

Patients with Parkinson's disease (PD) often compensate for their motor deficits by guiding their movements visually. A wide range of ocular and visual disorders threatens the patients' ability to benefit optimally from visual feedback. These disorders are common in patients with PD, yet they have received little attention in both research and clinical practice, leading to unnecessary – but possibly treatable – disability. Based on a literature search covering 50 years, we review the range of ocular and visual disorders in patients with PD, and classify these according to anatomical structures of the visual pathway. We discuss six common disorders in more detail: dry eyes; diplopia; glaucoma and glaucoma-like visual problems; impaired contrast and colour vision; visuospatial and visuoperceptual impairments; and visual hallucinations. In addition, we review the effects of PD-related pharmacological and surgical treatments on visual function, and we offer practical recommendations for clinical management. Greater awareness and early recognition of ocular and visual problems in PD might enable timely instalment of tailored treatments, leading to improved patient safety, greater independence, and better quality of life.

Key points
- Patients with Parkinson's disease are highly dependent on visual feedback to compensate for their motor deficits.
- Visual and ocular disorders are common in patients with Parkinson's disease.
- Early recognition and treatment of visual problems in Parkinson's disease are necessary to improve patient safety, independence and quality of life.
- We conducted a literature search covering 50 years
- We present an overview of the epidemiology, pathophysiology, diagnostic work-up and treatment of six common ocular and visual disorders in patients with Parkinson's disease.

Introduction

Parkinson´s disease (PD) is a common neurodegenerative disorder characterized by a wide range of motor and non-motor symptoms. The cardinal motor features (tremor, rigidity, bradykinesia, postural instability) (1) and non-motor features (e.g. disorders of mood and affect, cognitive decline, sensory dysfunction, autonomic failure (2), and visual hallucinations (3, 4)) have received considerable attention. However, a broad spectrum of ocular disorders (affecting the eyes or eyelids) and visual disorders (including central visual perception) has, despite being supposedly common in PD (4, 5), remained largely out of focus both in research and clinical practice.

Why recognition of visual disorders is important

A better awareness and timely recognition of visual symptoms in PD is important for several reasons. First, recognition of visual symptoms allows for closer determination of disease prognosis. For instance, visuospatial impairment is an important predictor of dementia in PD, and visual hallucinations for admission to a nursing home (6). Second, ocular and visual disorders can have a disabling impact on activities of daily living such as walking, reading or driving (7), forcing Parkinson patients to reduce their social and physical activities, resulting in a decreased quality of life (8). The impact of ocular and visual disorders is particularly vexing for patients with PD, because they typically have problems with internally guided movements and postural control, which they can compensate for by guiding their movements visually (9, 10). As an illustration: over 80% of PD patients who fell within a one-year timeframe were visually impaired, compared with 66% of non-fallers (11). Another example is freezing of gait, a debilitating symptom that is prevalent in advanced stages of PD. Visual cueing, e.g. in the form of stationary stripes pasted onto the floor, is an evidence-based neurorehabilitation technique to alleviate freezing of gait (12, 13), but is difficult to employ in the presence of ocular and visual disorders. Also new neurorehabilitation strategies such as exergaming, cueing via smart glasses or personalized neurorehabilitation in the home-situation through telemedicine (14, 15) cannot be benefited from when visual function is insufficient. Timely recognition of ocular and visual disorders is therefore essential, so that

tailored treatment can be installed to prevent complications such as falls or injuries, to restore mobility, to enhance the efficacy of visual cueing and various other non-pharmacological interventions, to ascertain a greater independence, and to improve the patient's quality of life.

The assessment of specific ocular and visual disorders also has value for the differential diagnosis of a hypokinetic-rigid syndrome, helping to separate patients with PD from those with a form of atypical parkinsonism such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) (5). However, this diagnostic aspect is not discussed in this review. Instead, we here provide a detailed, interdisciplinary overview of various ocular and visual disorders in PD.

Search strategy and selection criteria

We performed a systematic literature search in the databases PubMed, Medline and the Cochrane library and searched for relevant articles published between 1966 and January 2017. Search terms included: "visual", "ocular", "vision", "ophthalmologic", "eyes", "eyelid", "cornea", "retina", AND "Parkinson's disease". The results of the systematic literature review were supplemented by references acquired from the reference lists of included papers.

Ocular and visual disorders and PD

We have classified the various ocular and visual disorders in PD according to the anatomical structures that are involved in normal vision (Figure 1 and Table 1). Some of these disorders are due to the neurodegenerative process underlying PD, and these often respond positively to dopaminergic medication (Table 2). On the other hand, ocular and visual disorders can be side effects of dopaminergic, cholinergic or noradrenergic medication, and of surgical interventions like deep brain stimulation (DBS) and pallidotomy (Table 2).

Given the widespread dysfunction along the visual pathway in PD, it is not feasible to fully elaborate on every ocular and visual disorder. Instead, we will discuss six common and disabling ocular and visual problems in more detail.

These conditions include: dry eye disease; oculomotor disturbances and diplopia; glaucoma and glaucoma-like visual field loss; colour and contrast impairment; visuospatial and visuoperceptual impairments; and visual hallucinations. Recommendations for the management of these and other ocular and visual disorders are summarized in Table 3.

Table 1. Ocular and visual abnormalities in PD, classified by anatomic localization

		Ocular and visual finding in PD	Reference(s)
1	Oculomotor disturbances*	Impaired convergence	(5, 16-20)
		Diplopia	(10, 18, 19, 21)
		Bradykinesia and hypokinesia of ocular pursuit	(22, 23)
		Impaired vertical gaze**	(23, 24)
		Saccadic abnormalities #	(25)
		Disturbed smooth ocular pursuit movements	(22, 26)
		Ocular tremor	(27, 28)
		Dyskinetic eye movements	(29)
2	Eyelid	Decreased blink rates	(5, 30, 31)
		Apraxia of eyelid opening	(5, 32)
		Blepharospasm	(5, 33)
		Eyelid retraction	(23)
		Ptosis of superior eyelid	(23)
		Meibomian gland disease	(31)
3	Tear ducts/ apparatus	Decrease in tear secretion, resulting in dry eyes	(5, 17, 31, 34, 35)
4	Cornea	Decreased corneal sensitivity	(31)
5	Lens	Increased frequency of moderate/marked nuclear cataract in Parkinson's disease with dementia	(19)
		More prominent intensity of posterior subcapsular cataract	(17)
6	Pupil	Pupillary adaptation disturbances	(23, 36)
7	Retina	Retinal nerve fibre layer thinning	(37-44)

		Decreased contrast sensitivity	(10, 17, 44-46)
		Impaired colour discrimination	(10, 17, 45, 47-50)
8	**Macula lutea**	Reduced macular volume	(51)
		Thinner and broader mean foveal pit	(52)
9	**Optic nerve**	Higher incidence of glaucoma (optic nerve neuropathy) and glaucomatous-like visual field defects	(17, 53, 54)
10	**Cortex**	Visual hallucinations	(5, 10, 19, 55-58)
		Visuospatial deficits	(10, 59)
		Impaired facial expression recognition	(60)

* Anatomic localization where ophthalmologic abnormality can be seen/tested. ** impaired vertical gaze, with abnormalities of upward gaze slightly more frequent than abnormalities of downward gaze. # longer reaction times, multiple step, hypometric saccades, frequent square wave jerks.

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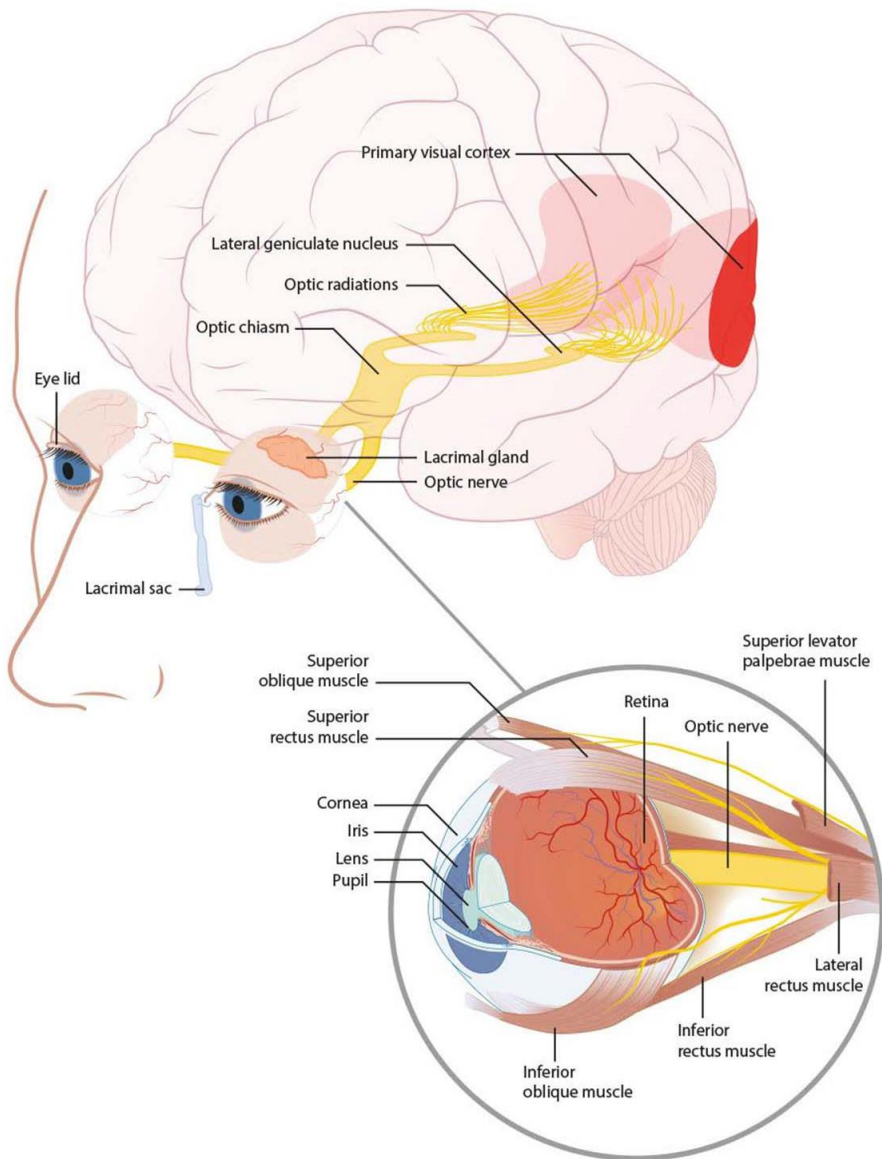
Figure 1. Overview of the visual pathway. Areas of interest linked to table 1 are attenuated.

Table 2. Effect of Parkinson treatment on visual functioning in Parkinson's disease

Negative side effects

Drug	Ocular and visual side effect	Best level of evidence	Reference(s)
Levodopa	Ocular dyskinesias	B	(61, 62)
	Eyelid melanoma	C	(63)
	Mydriasis, followed	D	(64)
	later by miosis	D	(64)
	Lid ptosis	D	(64)
	Blepharospasm		
Cabergoline	Reduced contrast sensitivity	B	(65)
Bromocriptine / dopamine agonists	Exacerbation of visual hallucinations	B-D	(64, 66)
Amantadine	Bilateral corneal	B-D	(67-72)
	endothelial	D	(67, 68)
	dysfunction	D	(64)
	(oedema)	D	(64)
	Superficial keratitis	D	(64)
	Mydriasis	C	(73)
	Reduced		
	accommodation		
	Visual		
	hallucinations		
	Blurred vision		

Benzhexol	Mydriasis and	C	(64, 74)
	increased risk for	D	(64)
	angle-closure	D	(64)
	glaucoma	D	(64)
	Photophobia	D	(64)
	Decreased	D	(64)
	accommodation		
	Dry eyes		
	Anisocoria		
	Blurred vision		
MAO-B inhibitors	Blurred vision	D	(64)
Dopamine-blocking agents	Oculogyric crises	C	(75)
Imipramine	Mydriasis	D	(64)
	Cycloplegia	D	(64)
	Dry eyes	D	(64)
	Ocular muscle	D	(64)
	paresis	D	(64)
	Nystagmus		
Deep Brain Stimulation (DBS) Stimulated area	**Ocular and visual side effect**	**Best level of evidence**	**Reference**
Nucleus subthalamicus (STN)	Visual hallucinations	C	(76)
	Vertical diplopia from skew deviation and ipsiversive binocular torsion	C	(77)
	Contraversive eye deviation	C	(78)
	Reduced voluntary ipsilateral gaze	C	(79)
	Apraxia of eyelid opening	C	(80-82)

	Involuntary closure of eyelid	C	(83)
	Fixation instability	C	(84)
	Torsional nystagmus	C	(81, 85)
	Unilateral mydriasis	C	(81)
Nucleus Pedunculopontine (PPN)	Oscillopsia	C	(86)

Area pallidotomy	*Ocular and visual side effect*	*Best level of evidence*	*References*
Globus pallidus interna (GPi)	Visual field defects	C	(87)
	Disturbed ocular fixation	C	(88)
Bilateral contemporaneous Posteroventral pallidotomy (PVP)	Apraxia of eyelid opening	C	(89)
Posteroventral pallidotomy (PVP)	Homonymous hemianopia	C	(90)

Therapeutic effects

Drugs	*Ocular and visual finding*	*Best level of evidence*	*Reference*
Levodopa	Normalization of dopamine in retina	B	(91)
		B	(92)
	Improves ocular pursuit movements	D	(93)
		D	(94, 95)
	Increased blink rate		
	Improves contrast sensitivity		

Apomorphine	Improves contrast sensitivity	C	(96)
	Improves ocular pursuit movements	B	(26)

Levels of evidence: A1 - Systematic review or meta-analysis containing at least some trials of level A2 and of which the results of the trials are consistent. A2 - Randomized comparative clinical trials of good quality (randomized double-blind controlled trials) of sufficient size and consistency. B - Randomized clinical trials of moderate (weak) quality of insufficient size or other comparative trials (non-randomized, cohort studies, patient-control studies. C – Non comparative trials. D – Expert opinion.

Table 3: Recommendations for management of ocular and visual disorders.

Ocular and visual symptom	Possible management options
Impaired convergence	Based-in prism Adapted glasses
Diplopia	Adapted prisms, convergence exercises (in convergence insufficiency)
Saccadic and ocular pursuit abnormalities	Optimal dopaminergic treatment
Decreased blink rates	Patient-awareness
Apraxia of eyelid opening	Brow lifting; deep brain stimulation
Blepharospasm	Botulin injections
Dry eye disease	Artificial tears and blinking advice
RNFL thinning	Control for visual field loss and glaucoma
Decreased contrast and / or colour sensitivity	Enough ambient light, filter glasses Optimal dopaminergic treatment
Glaucoma and glaucomatous-like field deficits	Regularly testing with Donder's test and timely referral to ophthalmologist
Visual hallucinations	Check for triggers in other drugs and comorbidity. Consider Charles Bonnet syndrome. Atypical neuroleptics when needed. Include addition cholinesterase inhibitors in dementing PD patients with visual hallucinations
In general	In house adjustments to prevent falling Explanation about decreased contrast while driving at night

1. Dry eye disease

Dry eyes disease ('keratoconjunctivitis sicca') is common in PD, with an estimated prevalence of 53-60% (5, 17), which is higher than the estimated prevalence of 5-35% in the general population aged 50 years and above (97). Dry eyes in PD are thought to result from a decreased blink rate, which is a classical feature of PD. A decreased blink rate leads to a diminished distribution of the lipid components of the tear film over the cornea (31, 34), causing the aqueous component to evaporate faster. In addition, dry eyes in PD may result from decreased tear production caused by autonomic dysfunction, based on the partial parasympathetic autonomic innervation of the lacrimal gland (34).

During history taking, one should not only ask for dry eyes, but also for associated typical symptoms such as burning sensations of the eyes, intermittent lacrimation (e.g. tearing), blurred vision, a gritty or sandy sensation, red eyes, or the feeling of pressure or even pain behind the eye balls or around the orbit. Dry eyes can also be objectively verified by the Schirmer's test, reflecting the amount of aqueous tear production; and the 'tear breakup time', measuring the stability of the tear film layer (5, 34) (see the Appendix).

Symptomatic treatment of dry eyes is challenging (Table 3) and has not been studied specifically in PD patients. Patients can be advised to consciously increase their blink frequency, but this is difficult to achieve, because they are usually not aware of this. Artificial tears (eye drops) are the current mainstay of treatment, often resulting (98) in a significant reduction of discomfort and better visual acuity, although PD-related motor impairments might impede their self-administration. In addition, oral supplementation with polyunsaturated fatty acids (omega-3 and omega-6) might relieve symptoms (98, 99). Semi-permanent occlusion of the tear ducts by silicone or collagen plugs, or permanent occlusion by thermal cautery or argon laser can provide symptomatic relief of severe dry eyes, at the price of potential side effects as epiphora (overflow of tears), foreign body sensation, eye irritation, and spontaneous plug loss (100).

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2. Oculomotor disturbances and diplopia

Various oculomotor disturbances are associated with PD, including convergence insufficiency (16-20), abnormal saccades and smooth pursuit (23, 101-103), and up-gaze limitation (23). Convergence insufficiency is supposedly highly prevalent in PD, and may cause blurred near vision (and thus disturb reading) and diplopia (18).

The prevalence of diplopia in PD has only been studied in small cohorts, which reported a prevalence varying between 10-30% in PD patients, compared to 1-19% in controls (4, 5, 19). The incidence of diplopia in PD increases with disease progression (19). Diplopia is more common in patients with pre-existent ocular misalignment and with daytime somnolence, suggesting that non-drowsy patients can to some extent compensate for ocular misalignment (19).

The pathophysiology underlying diplopia in PD remains unclear. Diplopia due to convergence insufficiency may improve with dopaminergic therapy (16), suggesting that dopamine deficiency in the basal ganglia takes part in its pathophysiology. However, it has also been suggested that convergence insufficiency is due to extranigral pathology (18). Selective diplopia, a phenomenon where isolated (instead of all) objects or persons are perceived duplicated, has been associated with the presence of dementia, visual hallucinations, changes in antiparkinsonian treatment, and subtle oculomotor disturbances, although a pathophysiological mechanism closer to that of visual hallucinations than to oculomotor disturbances is expected (21, 104).

A comprehensive neuro-ophthalmologic work-up of patients with PD is useful to evaluate oculomotor disturbances (105). Diplopia can be constant, but more often it is only present in specific situations, e.g. while reading or when looking nearby. It is therefore important to ask for activities that provoke diplopia. The first diagnostic step is to differentiate between monocular and binocular diplopia (appendix), because monocular diplopia is not caused by PD pathology, but rather suggests ocular media opacities like cataract or a major refractive error of that particular eye. Several tests can detect ocular misalignment, like the 'Hirschberg corneal reflex test', the 'cover test' and the

'cover/uncover test', or more advanced techniques used by (neuro-)ophthalmologists, or eye care practitioners (appendix). Gaze restriction is best detected by clinical examination (20). Saccades can be examined using video-oculography, to determine amplitudes and latencies (as a measure of ocular bradykinesia).

The treatment strategy of diplopia depends on the underlying mechanism. For example, convergence insufficiency can be treated with base-in prism and convergence exercises (5, 18). Because ocular motor function may improve with dopaminergic treatment (92, 101), OFF-periods should be minimized. In patients with hallucinations, selective diplopia might improve when treating the hallucinations.

3. Glaucoma and glaucoma simulating optic neuropathy

Glaucoma is a progressive optic neuropathy in which increased retinal nerve fibre apoptosis leads to thinning of the neuro-retinal rim of the optic disc, increasing the central excavation (Figure 2) (106). This causes a characteristic arcuate-shaped visual field defect, which starts in the mid-periphery, and slowly progresses to the periphery and centre. Patients are generally not aware of the visual field defect (negative scotoma) until central defects appear. An increased intraocular pressure (IOP; >21 mmHg) is the main risk factor for developing glaucoma, but in about one third of patients the IOP is not increased and they are diagnosed with normal-pressure glaucoma. In open angle glaucoma, the irido-corneal angle is open, but aqueous outflow is diminished, slowly leading to visual field defects (106). In angle-closure glaucoma, an immediate occlusion of the anterior chamber leads to blockage of aqueous outflow, resulting in a red, painful eye with symptoms like nausea and vomiting (106).

Epidemiologic data on the association between glaucoma and PD are scarce. Two studies found a prevalence of glaucoma of 16-24% in PD compared with about 7% in controls (17, 53). Interestingly, in PD all cases concerned primary open angle glaucoma, while the prevalence of increased IOP was lower in PD patients than in controls (17, 53). Different hypotheses linking PD to open angle glaucoma have been proposed, involving retinal degeneration due to

progressive retinal dopamine depletion (107) and alpha-synuclein mediated axonal degeneration in both PD and glaucoma(107, 108). In addition, angle-closure glaucoma can occur due to blocked aqueous outflow, associated with dopaminergic and anticholinergic medication, especially in patients with a pre-existent narrow chamber, e.g. in high hypermetropia (Table 2) (74). However, future studies are needed to map the risk of developing glaucoma in PD patients and to unravel its pathophysiology.

Apart from glaucoma, patients with PD are at risk for visual field defects and retinal nerve fibre layer (RNFL) thinning not caused by glaucoma (43, 54). The underlying pathology is still unclear and requires further research.

During clinical examination, the Donder's confrontation method and Amsler grid (appendix) can be used as a screening tool for moderate to severe central and peripheral field defects. If visual field loss is suspected, the patient can be referred to an ophthalmologist for more specialized testing, including fundoscopy, the Humphrey visual field exam and measurement of the intraocular pressure using applanation tonometry (appendix). Quantitative information about optic nerve fiber cell loss can be obtained using recently developed methods like confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography (106).

In patients diagnosed with open-angle glaucoma, eye drops can be used to lower the production of chamber fluid or to increase the drainage of chamber water. If insufficient, drainage of chamber fluid can be enhanced by laser trabeculoplasty or trabeculectomy. Therapies other than those aimed at decreasing intra-ocular pressure, like neuroprotective therapy, have not yet been studied in sufficiently large clinical trials(109). In patients with closed-angle glaucoma, laser peripheral iridotomy is the first-line treatment to eliminate pupillary block (106).
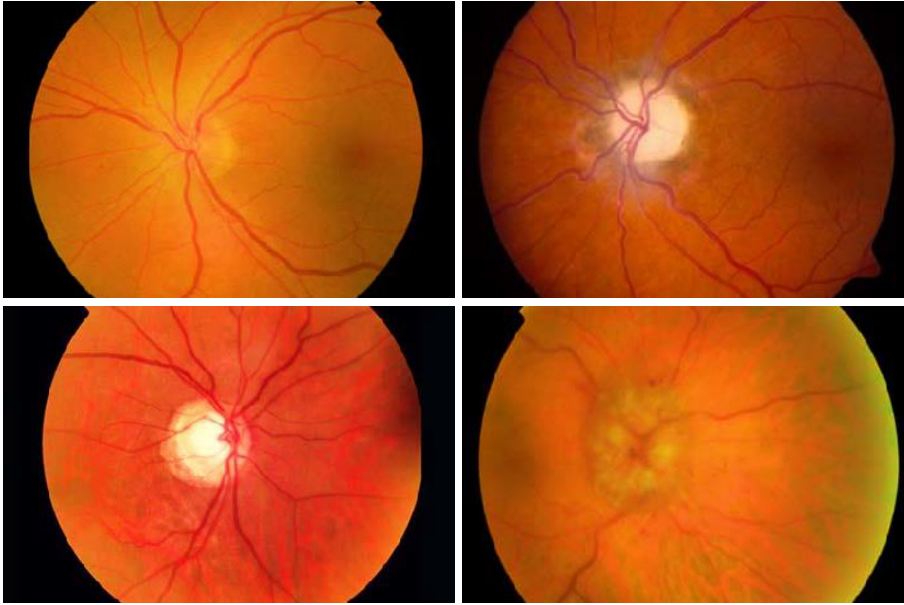
Figure 2. Funduscopic appearance of the optic nerve. A. Normal optic disc with sharp borders and no pallor. B. Optic disc atrophy. C. Glaucoma with typical cupping and peripapillary atrophy. D. Papiledema with hyperemia, unsharp borders and prominence of the optic disc.

4. Diminished contrast sensitivity and colour discrimination

Contrast sensitivity reflects the ability to differentiate luminance differences of objects and areas (94). Reduced contrast sensitivity can result in problems during situations with low light, e.g. when driving at night (7, 94). Colour discrimination is the ability to distinguish subtle differences in colour. Decreased contrast sensitivity and reduced colour discrimination, which can both be experienced early in the disease, are thought to be common in PD, but exact prevalence numbers are missing (17, 45). Which colour axis is mostly affected is still unclear though; both the blue-yellow (45, 50) and red-green axis(94, 110) have been suggested.

The pathophysiology of diminished contrast sensitivity and colour discrimination is not fully clear. Deficiency of retinal dopamine is thought to

result in impaired processing of visual stimuli, leading to decreased contrast sensitivity and colour discrimination (6, 45, 94). In addition, the primary visual cortex has been suggested as a source of contrast sensitivity deficits. Impaired colour discrimination has also been described to originate from a cortical origin, although these studies were prone to confounding by cognitive and motor deficits (6).

In clinical practice, contrast sensitivity can be tested with the Pelli Robson chart or with sine wave gratings at different spatial frequencies (appendix). To test colour discrimination, the Farnsworth-Munsell 100 Hue test (FM) and the D-15 Lanthony test (D-15) are most widely used(94) (appendix).

Both contrast sensitivity and colour discrimination have shown variable improvements with dopaminergic therapy (Table 3) (16, 94, 95), aimed at normalizing the amount of retinal dopamine(91). Blue haze (short-wavelength light) can veil the patient's view, so yellow filtering glasses may improve contrast sensitivity when patients experience glare (111). Selective absorption glasses, that may be applied as filter clips onto the patient's own spectacles, can be supportive. In addition, patients should be adviced to read and work with sufficient ambient light to create optimal visual circumstances. Finally, it is presumably wise to advise patients to avoid driving after dusk and before dawn.

5. Visuospatial and visuoperceptual impairments

Performance on several visuospatial tasks appears to be impaired in patients with PD (6, 10, 59). Amongst these are the perception of space(112, 113), recognition of line orientation (114, 115), mental three-dimensional rotation of objects(116), identification of figures embedded in complex figures (117), visuospatial problem solving(118, 119), depth perception (120) and spatial working memory (121). In addition, visuoperceptual impairments in the detection of motion (122) human movement (123, 124) and facial recognition (6, 125-127) have been observed in PD.

Visuospatial impairments in PD have been associated with freezing of gait (128) and dementia (59, 129), but may be common in non-demented PD patients as well. In answer to a self-report questionnaire, 40% of 55 non-

demented PD patients reported difficulties in estimating spatial relations, and 50% reported bumping into doorways (10). Otherwise, few epidemiologic data on visuospatial and visuoperceptual impairments in PD are available.

The pathophysiology of these problems likely resides within the cortex. Indeed, the primary visual cortex is probably involved in processes such as distinguishing between lines with different orientations (6). Moreover, impairments in higher order visuospatial and visuoperceptual processing in PD have been associated with grey matter atrophy in temporo-parietal cortical regions (130, 131).

In clinical practice, visuospatial impairments may lead patients into bumping into doorways or objects, and to experience problems driving a car and navigating (10). Visuospatial function can easily be assessed by asking the patient to draw two intersecting pentagons (130), a clock or a house, but it should be kept in mind that these tests are also influenced by cognitive domains other than visuospatial function (6, 122). Validated bedside tests for visuoperceptual impairments are not yet available.

It is important to raise awareness amongst patients, carers and healthcare workers about the possible presence of visuospatial and visuoperceptual impairments in PD. When visuospatial impairments are suspected, it is advised to refer patients for a driving assessment. Tactical driving skills, such as visual scanning, can be trained with driving rehabilitation strategies (132).

6. Visual hallucinations

Visual hallucinations are defined as the perception of an object or event, in the absence of an external stimulus. The visual hallucinations considered in this manuscript comprise simple and complex visual hallucinations, visual illusions and passage of shadows (4). Visual hallucinations early in the disease course are a typical feature of Lewy body parkinsonism (i.e. PD with dementia (PDD) or dementia with Lewy bodies), differentiating these two conditions from other types of parkinsonism (58).

The estimated prevalence of visual hallucinations in PD ranges between 4-82.7% (4, 17, 55), depending on the method of assessment and the definition

of visual hallucinations (e.g. illusions included or excluded) used, the patient selection (e.g. disease stage and cognitive impairments), and the (cross-sectional or longitudinal) set-up of studies. Longitudinal studies (55, 56) report a prevalence of around 60%, which makes visual hallucinations a core non-motor symptom (4, 55). Visual hallucinations are important predictors for future development of dementia and nursing home admission (3, 55). Once visual hallucinations exist, they will persist and progress, unless adequately treated (56).

Visual hallucinations have a multifactorial aetiology, being associated with low visual acuity, longer disease duration, impaired contrast sensitivity, REM sleep behaviour disorder and reduced colour discrimination (5, 104). They are often seen in patients with a higher age and cognitive decline or dementia (5, 133). In addition, dopaminergic drugs (dopamine agonists more so than levodopa or monoamine oxidase (MAO)-B inhibitors) and drugs with a(n) (partial) anticholinergic working mechanism (such as anticholinergics and amantadine) are important triggers (Table 2) (57, 133). However, recent studies suggest that the causal role of medication in the pathophysiology of visual hallucinations in PD is smaller than previously thought, and that visual hallucinations are mainly due to underlying disease pathologies themselves. Various mechanisms underlying visual hallucinations in PD have recently thoroughly been discussed in an excellent review by Weil and colleagues (6) and are not discussed here.

In clinical practice, it is important to ask explicitly for the presence of visual hallucinations, because they are among the most common "non-declared" symptoms (i.e. they are often not reported spontaneously by patients themselves) (134). In some cases, visual hallucinations can improve by simplifying or reducing antiparkinsonian medication (57). Drugs with high risk-benefit ratios (i.e. high risk of cognitive side effects vs relatively low anti-parkinsonian efficacy) should be tapered first; including anticholinergics, anti-N-methyl-D-aspartate (NMDA) antagonists, and MAO-B inhibitors. If this is insufficiently effective, the next step is to reduce dopamine agonists, and finally to reduce levodopa (133). It is not always feasible to achieve a dose reduction of dopaminergic drugs to a level that leads to resolution of psychotic

symptoms because of an unacceptable increase in motor disability. Initiation of anti-psychotic therapy may be necessary. Clozapine is the only drug with evidence from randomized controlled trials showing a clear efficacy in treating hallucinations in PD (135). In clinical practice, many physicians prefer to try quetiapine first, hoping to avoid the small but definite risk of agranulocytosis (133). However, randomized trials have failed to clearly support quetiapine's efficacy (135). The new serotonergic drug pimavanserin has shown promising results in phase III studies and has recently been approved in the US for the treatment of hallucinations and delusions in PD (136).

Conclusion and future perspectives

The spectrum of ocular and visual disorders occurring during the course of PD includes all levels of visual processing. Many of these ocular and visual disorders occur more frequently in PD than in the general population, either because of a relation with the PD-related pathology, or because Parkinson-related medication negatively affects the visual system. Importantly, the presence of ocular and visual disorders has great implications for clinical management, because due to their defective motor planning and – programming, patients with PD are particularly dependent on visual feedback to improve the quality and safety of their movements. Also, many current neurorehabilitation strategies rely on sufficient visual function. Therefore, these strategies should be adapted to also fit visually impaired patients with PD, so they can also benefit from these interventions.

Another important message is that the association between ocular symptoms and PD is far from obvious to both patients and clinicians in clinical practice: many patients may not adequately report ophthalmic problems themselves, while clinicians frequently miss ocular disorders that – in many cases – can be treated. This results in a delayed diagnosis and further deterioration of the visual disorders. And most importantly, it leads to suboptimal treatment, unnecessary disability and a compromised quality of life. We therefore strongly encourage clinicians involved in PD care to routinely ask their patients about ocular symptoms and to take action if ocular symptoms are suspected, e.g. by referring their patient to an ophthalmologist. We also advise clinicians to remember that dopaminergic medication, as well as DBS and

pallidotomy, can contribute to visual problems. As such, when patients experience sudden visual problems after alterations in medication or surgical interventions like DBS or pallidotomy, evaluation of the new treatment strategy is required. Finally, we conclude that specific evidence on ocular and visual problems in PD and their treatment in clinical practice is still lacking. Much more work remains needed to determine the exact incidence and prevalence of PD-related ocular and visual disorders, to further map the burden of these ocular and visual problems for PD patients, and to create more insight into the underlying pathophysiology. Based on this, tailored interventions can be developed, leading to improved patient safety, greater independence and better quality of life and quality of care.

Appendix

Supplementary Table 1. Ophthalmologic testing

Dry eye disease testing

- **Schirmer's test**
  A small stroke of filter paper is applied for a certain amount of time, mostly five minutes. The paper changes colour depending on the amount of tear fluid.

- **Tear break-up time**
  The tear film stability, e.g. the interval between a last complete blink and the break-up of the tear film, is studied with a slit-lamp. Fluorescein is applied in the lower fornix, followed by several eye blinks. The time between the last blink and the first appearance of a dark spot (dry area) on the tear film is called the tear break-up time. When this time is less than 10 second it is suggestive for dry eye disease.

Diplopia / ocular misalignment testing

- **Monocular / binocular diplopia test**
  One eye is covered. Double images will disappear in binocular diplopia, but persist in monocular diplopia.

- **The Hirschberg corneal reflex test**

A simple test to show ocular misalignment. An examiner shines with a light in both eyes while the patient looks straight forward and then explores if both reflex lights are in the centre (137).

- **The "cover test" and the "cover/uncover test"**
These tests can reveal less obvious ocular misalignment by demonstrating latent strabismus. The cover test evaluates if the eye makes a corrective movement after the covered eye is quickly uncovered (just once). The cover/uncover test also evaluates corrective movements after coverage, but uses multiple fast cover/uncover moves.

Convergence testing

- **Base-out prisms**
The convergence amplitude can be measured by letting the patient fixate on a small letter while putting base-out prisms of increasing dioptres before one eye until the patient reports double vision or blurred vision.

- **Accommodation ruler**
The near point of convergence can be evaluated by an accommodation ruler. A standard reading card is approximated to the patient's eyes with and without reading correction on the ruler until the patient reports blurred or double vision and one eye deviates outward.

Glaucoma testing

- **Donder's confrontation test**
A patient is requested to stare at the nose of the examiner while the examiner places his both hands in the middle between himself and the patient but in the corners of the patient's visual fields. The examiner then alternately moves one or both. The patient is asked to tell or point out which hand(s) he sees moving. The examiner uses his own visual fields as reference.

- **Amsler grid**
Black or white square with straight vertical and horizontal contrasting lines (e.g. in a black square white lines, in a white square black ones), dividing the square in a sort of checkerboard with little squares. When

patients see an incomplete appearing checkerboard, this requires further investigation.

- **Optical coherence tomography (OCT)**
  In this medical imaging technique, light is used to create 3D images from optical scattering media like the retinal pigment epithelium, choroid and nerve fibre layers. Neuro-regenerative changes leading to pseudo-glaucomatous disc cupping mostly show pallor of the temporal part of the optic disc. One may use OCT to help with the differential diagnosis of optic disc cupping. This technique shows early loss of retinal nerve fibres in the temporal part of the optic disc in neurodegenerative disorders, which is not typical for early glaucoma (54, 138).

- **Humphrey field exam**
  A patient is shown small appearing lights in all different visual fields and asked to respond if he or she sees it. With these responses his visual field is built up (automated perimetry).

- **Fundocopy**
  Fundoscopy uses an ophthalmoscope to look at the optic nerve and retinal vessels. By funduscopy one may distinguish between different kinds of optic nerve head diseases, such as optic nerve atrophy (partial of complete), glaucomatous damage, and optic nerve head oedema (Figure 3).

- **Intraocular pressure (IOP)**
  IOP can be measured using applanation tonometry as the force that is required to applanate (flatten) a constant area of the cornea. The intraocular pressure is mostly raised in open-angle glaucoma (139).

Contrast sensitivity testing

- **Pelli Robson chart**
  Normal acuity charts use perfectly black ink on perfectly white paper, achieving near 100% contrast. Pelli Robson charts use alternating light and dark bars at varying intensity to test how sensitive the difference between those bars can be seen.

Colour discrimination testing

To test colour discrimination, many test can be used. The pseudochromatic plate test is widely used. Patients have to look at different plates that look like mosaics. Not-colour blind persons are able to see a "hidden" number in this mosaics. The Farnsworth-Munsell 100 Hue test (FM) and the D-15 Lanthony test (D-15) are other tests, in which patients must arrange colours in a fluently order (94).

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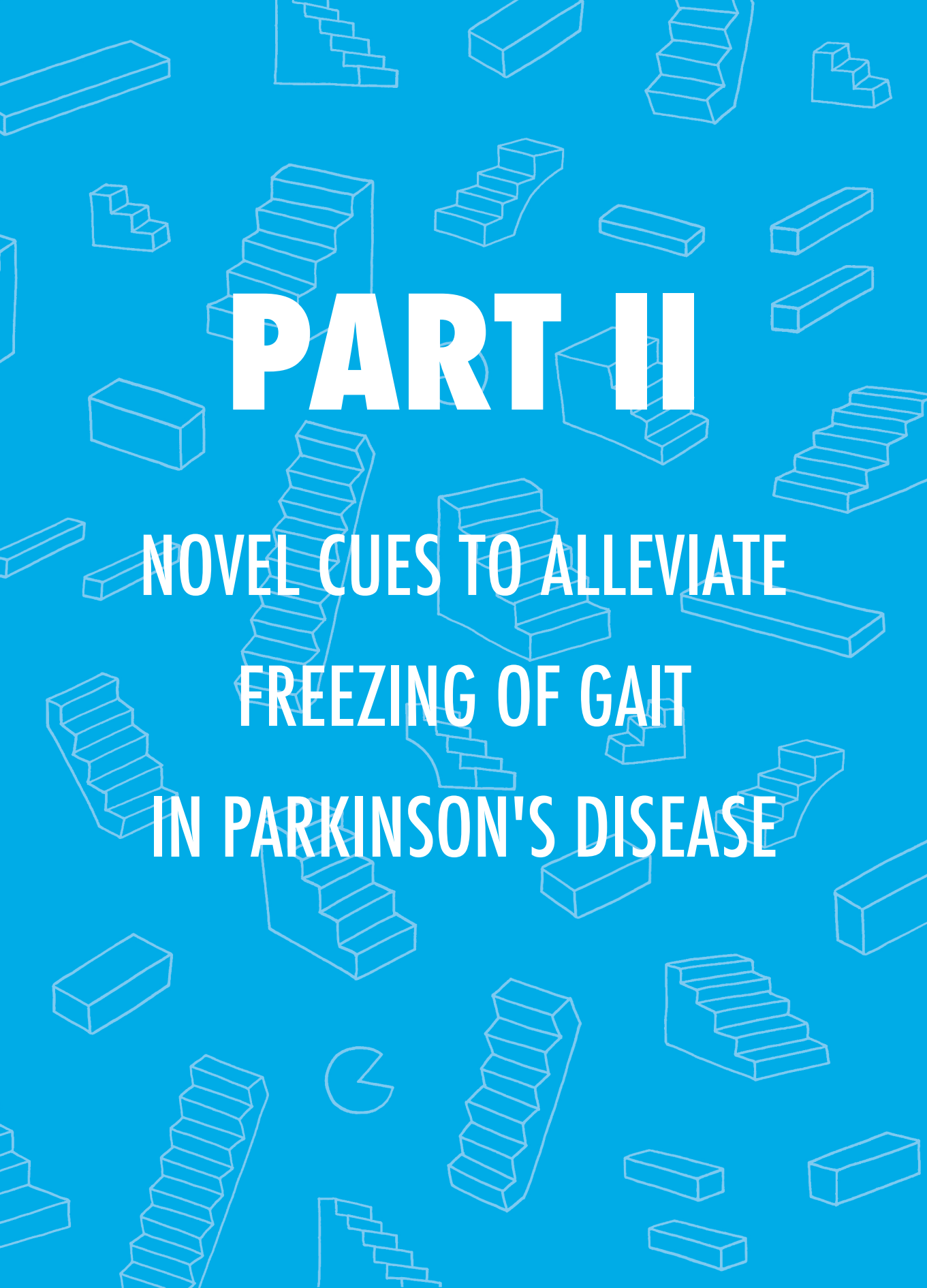63.	Haider SA, Thaller VT. Lid melanoma and parkinsonism. Br J Ophthalmol. 1992;76(4):246-7.

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PART II

NOVEL CUES TO ALLEVIATE

FREEZING OF GAIT

IN PARKINSON'S DISEASE

CHAPTER 4

'SUPERFICIAL BRAIN STIMULATION'

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BLOEM, B.R.

Gait impairments are common and debilitating in patients with Parkinson's disease (PD). One particularly debilitating type of gait impairment is freezing of gait (FOG), which is characterized by sudden episodes during which patients feel as if their feet 'are being glued to the floor' (1). Presumed mechanisms underlying gait impairment in PD involve dysfunction of the basal ganglia, which enable automatic performance of overlearned movements such as gait. In PD, basal ganglia dysfunction results in reduced automaticity and a reduced ability to internally generate movements (i.e. patients experience more difficulty producing movements in the absence of an external cue) (2). However, many PD patients spontaneously develop strategies to compensate for their reduced automaticity and inability to internally generate movements (3). Understanding such compensatory mechanisms is important, e.g. to shape focused rehabilitation techniques and to unravel the mechanisms underlying gait impairments in PD. Here, we present a patient who spontaneously presented several compensatory strategies to overcome FOG, including one very unusual "trick".

A 65-year old man was seen at our outpatient clinic. PD had been diagnosed 20 years earlier. Because of his young age at disease onset and a positive family history for PD, genetic testing was performed, revealing two PARK2 gene mutations (c.994T>C variant and an exon 6 duplication). His main symptom was FOG; he did not have any cognitive impairments. He experienced FOG at least once a day. FOG episodes were more frequent and longer in duration when dopaminergic medication had worn off. Marked FOG was typically provoked by gait initiation and turning (video 1; signed consent for publishing these videos was provided). The patient presented three self-invented compensatory strategies to improve his gait, one of which was unusual. Specifically, the first strategy was to gently press the index fingers bilaterally onto his temples, which effectively and consistently relieved FOG, and which in fact also helped to prevent FOG from occurring (video 2). This successful strategy had become so deeply embedded in his daily routine that he repeatedly showed this behaviour, even when asked to suppress this. Both other strategies were more mainstream, and have been described before (4). The second was to pretend as if he was ice-skating (video 3). The third strategy

was lifting up his knees high during walking, as if he was climbing a staircase (video 4).

We can only speculate about the mechanisms that might underlie the unusual strategy of 'superficial brain stimulation' (achieved by pressing the temples) in this patient. One possible explanation is that the temple pressing enabled him to focus on the task at hand. Alternatively, pressing the temples might act as an external somatosensory cue that facilitates gait initiation. The temple pressing would then represent a single cue, unlike rhythmic cues offered by e.g. a metronome. Indeed, the patient's gait did not worsen after releasing his index fingers from the temples. Finally, we considered the possibility of a sensory trick, like the gentle touch to the cheek that can alleviate cervical dystonia. Certainly, dystonia is common in patients with autosomal recessive forms of parkinsonism, including PARK2 (5). However, we observed no dystonia in the lower limbs or elsewhere in the body. Also, sensory tricks are typically applied to the same body segment where the dystonia manifests itself (6). Taken together, we do not feel that the temple pressing represents a sensory trick.

Regardless of the exact explanatory mechanism, this case adds to the growing and rich repertoire of compensatory mechanisms that are discovered by patients. It would be interesting to share our present observation with other patients, to see if the temple pressing technique can be replicated. From a rehabilitation perspective, it is important to educate patients about the wide range of possible compensatory strategies, and to investigate which is most feasible for each individual.

The two other mechanisms (skating and knee lifting) represented examples of alternative motor programs that helped to overcome the reduced automaticity caused by basal ganglia dysfunction. Moving forward using skating movements is a much less overlearned motor program than regular walking, and is therefore presumably less dependent on automatized internal triggering by the basal ganglia. The same mechanism might apply to the high knee lifting strategy. Additionally, knee lifting might force the patient to make a larger lateral weight shift onto the stance leg prior to step initiation by the

contralateral (and now unloaded) foot. This would be helpful to alleviate FOG, because PD patients seem to have a reduced ability to integrate anticipatory postural adjustments with subsequent steps, which could well play a role in the pathophysiology of FOG (7).

Supplementary material

The online version of this article (doi:10.1212/WNL.0000000000003859; http://www.neurology.org/content/suppl/2017/03/15/WNL.0000000000003859.DC1) contains supplementary video material

Video legends
Video 1: Freezing of gait when starting to walk and when turning

Video 2: Pressing the temples to improve gait

Video 3: Making ice-skating movements to improve gait

Video 4: Lifting the knees high to improve gait

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CHAPTER 5

A PAINTED STAIRCASE ILLUSION

Abstract

We report a 60-years old man with Parkinson's Disease who experienced a remarkable alleviation of his freezing of gait when crossing a painted staircase optical illusion. Apparently, the *illusion* of visual cues can be sufficient to reduce freezing of gait. Also, it underscores an additional value of three-dimensional over two-dimensional visual cues in the reduction of freezing of gait. This observation opens doors to whole new fields of visual cues, for example delivery of visual cueing via augmented reality, which requires verification in future studies.

Introduction

Freezing of gait (FOG) is common in people with Parkinson's disease (PD) or a form of atypical parkinsonism. Patients describe FOG as a sudden and often unexpected experience as if their feet 'are being glued to the floor' (1, 2). FOG is a major cause of falls, and has a debilitating impact on quality of life (1, 2). An example of a non-pharmaceutical intervention is the use of visual cues, e.g. stationary lines pasted at fixed distances onto the floor, or laser lines projected onto the floor, allowing patients to take externally guided steps (2). A subgroup of patients only shows a selective improvement of FOG with three-dimensional (3D) visual cues, but not with two-dimensional (2D) cues (3). In this video-supported case report, we present a patient for whom the *illusion* of a 3D cue was sufficient to alleviate FOG.

Case report

A 60-years old Indian man was diagnosed with PD at the age of 45 years. At disease onset he experienced a right-sided tremor, rigidity and occasionally FOG. With disease progression, the occurrence of FOG increased, to eventually more than once a day. Episodes of FOG were provoked by turning and gait initiation, and presented most commonly and severely when levodopa had worn off. FOG significantly affected his daily activities, due to reduced mobility, feelings of insecurity and fear of falling (video 1). His FOG was resistant to 2D visual cues like transverse lines and checkerboard tiles. Interestingly, FOG rarely occurred when climbing stairs (video 2). This observation inspired a relative – a professional product designer by background – to paint a staircase with a 3D optical illusion onto the floor of his house (video 3). FOG was markedly alleviated when the patient walked across this painted staircase illusion, with FOG instantly recurring at the end of the painting.

Discussion

This is a remarkable example of a patient whose FOG was alleviated by visual cues presented as a 3D illusion, whereas 2D visual cues were ineffective. Because only the actual and illusionary staircases were effective strategies, we consider the role of a (subjective) third dimension crucial in this patient.

Several hypotheses explain why, in some patients, 3D cues are more effective than 2D cues (3). First, compared to 2D cues, 3D cues may require patients to lift their feet higher, thereby activating alternative motor programs which might be better preserved (3). Second, FOG is possibly caused by an impaired ability to make a lateral weight shift onto the stance leg preceding a step by the contralateral (and now unloaded) leg (4). 3D cues likely trigger patients to make a larger lateral weight shift (4). Third, 3D cues may provide a stronger activation of cortical visual areas than 2D cues, resulting in a stronger visual compensation for the compromised axis between the basal ganglia and supplementary motor area (3).

Although potentially effective, painted 3D illusions likely have limited usability because they can only be applied within the patient's own home, and would have a large impact on the aesthetics of the living area. However, attractive alternatives appear at the horizon. 3D cue-illusions may in future be provided via augmented reality, enabled by modern technologies like smart glasses (5, 6). Next, combining augmented reality with wearable sensors could allow for effective 3D cueing in an on-demand manner (5, 7). However, these hypotheses require verification in future studies.

Finally, we regard this case description as a homage to the inventiveness of patients and their caregivers. Our observation underscores the need for close collaboration between patients, relatives and clinicians in order to optimize care for the often severely disabled patients with PD.

Supplementary material

The online version of this article (doi:10.1007/s00415-016-8195-z; https://link.springer.com/article/10.1007%2Fs00415-016-8195-z#SupplementaryMaterial) contains supplementary material.

Video legends

Video 1: 60-years old man with Parkinson's disease and severely disabling freezing of gait.

Video 2: The same patient demonstrating a preserved ability to climb stairs.

Video 3: Demonstration of a painted three-dimensional staircase illusion alleviating freezing of gait.

All three videos were videotaped after each other (video 1 – 2 – 3), when levodopa had worn off and the patient experienced an OFF-phase.

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5

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In response to our recent case report in this journal, where we described a patient with Parkinson's disease (PD) for whom a painted illusion of a three-dimensional staircase was sufficient to relieve freezing of gait (FOG) (1), Gilat and al. performed a brilliantly simple and effective explanatory study. The investigators asked seven persons with PD and FOG to perform a timed up and go (TUG) task and to climb stairs, initially with their eyes open, and then with eyes closed. They reasoned that, if visual feedback was the dominant explanation for the painted staircase effect, then climbing stairs would worsen with eyes closed. The results showed that more FOG occurred during the TUG task while walking with the eyes closed compared to eyes opened, while no FOG occurred during staircase climbing, irrespective of eye closure.

We are thankful that our case report has inspired these researchers to further unravel the mechanisms underlying the phenomenon of preserved stair climbing in PD. We agree with Gilat and colleagues that enhanced visual feedback appears not to be the only compensatory mechanism through which climbing stairs can alleviate FOG. As pointed out before (1), other mechanisms are likely involved, including higher lifting of the feet and performing larger lateral weight shifts. Note that these alternative mechanisms apply in particular to the actual act of climbing stairs. Walking on a painted three-dimensional illusion of a staircase depended, by definition, on visual inspection of the painting.

We still feel that visual compensation might partially explain why climbing stairs is relatively preserved in PD. All participants in Gilat's study performed the tasks first with eyes open, allowing participants to obtain a visuospatial memory of the staircase, and then with eyes closed. Upon withdrawal of a perceived stimulus, specific aspects of that stimulus (such as orientation or motion) are maintained by the cortical areas that were involved in the initial processing of that stimulus (2). Therefore, visuospatial information obtained when observing a staircase, could be retrieved from 'storage' in the visual working memory of (parietal and visual) cortical areas when closing the eyes. An alternative phenomenon is that of visual imagery, where the time span between the visual stimulus and retrieval of the maintained representation is longer than for visual working memory. Visual imagery of a stimulus induces

a similar neural activation pattern as that generated by actual visual perception of that stimulus (2, 3). Therefore, although recruitment of visual working memory could be circumvented when performing eyes-closed trials before eyes-open trials, participants would still be able to generate an internal representation of a staircase through visual mental imagery. As such, climbing a staircase could provide a visual compensatory strategy either through direct visual perception (in eyes-open conditions) or indirectly through visual working memory and through visual mental imagery (in eyes-closed conditions).

Gilat et al. suggested that staircase climbing could be a more discrete motor task than overground walking, with overground walking being more dependent on attention and visual input, while climbing stairs would only require the initiation and execution of a motor plan. We raise a further explanation: namely that climbing stairs is less overlearned (and thus less automatized) than overground walking, and therefore being less dependent on the affected putamen (4). Indeed, FOG can be reduced by adopting a less overlearned walking pattern, for example by walking sideways ('crab gait') or by making 'ice-skating' movements. Finally, we would like to add that climbing stairs is a challenging and – particularly for patients with balance impairment – a potentially dangerous task, especially with eyes closed, possibly enhancing a participant's alertness and attention for the task, thereby improving its execution (5).

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CHAPTER 6

THREE-DIMENSIONAL AUGMENTED REALITY VISUAL CUES DELIVERED BY SMART GLASSES

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Abstract

External cueing is a potentially effective strategy to reduce freezing of gait (FOG) in persons with Parkinson's disease (PD). Case reports suggest that three-dimensional (3D) cues might be more effective in reducing FOG than two-dimensional cues. We investigate the usability of 3D augmented reality visual cues delivered by smart glasses in comparison to conventional 3D transverse bars on the floor and auditory cueing via a metronome in reducing FOG and improving gait parameters. In laboratory experiments, 25 persons with PD and FOG performed walking tasks while wearing custom-made smart glasses under five conditions, at the end-of-dose. For two conditions, augmented visual cues (bars / staircase) were displayed via the smart glasses. The control conditions involved conventional 3D transverse bars on the floor, auditory cueing via a metronome, and no cueing. The number of FOG episodes and percentage of time spent on FOG were rated from video recordings. The stride length and its variability, cycle time and its variability, cadence and speed were calculated from motion data collected with a motion capture suit equipped with 17 inertial measurement units. A total of 300 FOG episodes occurred in 19 out of 25 participants. There were no statistically significant differences in number of FOG episodes and percentage of time spent on FOG across the five conditions. The conventional bars increased stride length, cycle time and stride length variability, while decreasing cadence and speed. No effects for the other conditions were found. Participants preferred the metronome most, and the augmented staircase least. They suggested to improve the comfort, aesthetics, usability, field of view and stability of the smart glasses on the head, and to reduce their weight and size. In their current form, augmented visual cues delivered by smart glasses are not beneficial for persons with PD and FOG. This could be attributable to distraction, blockage of visual feedback, insufficient familiarization with the smart glasses or display of the visual cues in the central rather than peripheral visual field. Future smart glasses are required to be more light-weight, comfortable and user friendly to avoid distraction and blockage of sensory feedback, thus increasing usability.

Introduction

In advanced disease stages, most persons with Parkinson's disease (PD) experience freezing of gait (FOG): sudden paroxysmal gait arrests preventing effective forward movement (1, 2). FOG negatively impacts mobility and independence and is associated with falls, fall-related injuries and emotional stress in social situations, resulting in a reduced quality of life (3, 4). Tight turns, narrow passages, gait initiation and approaching a destination are well-known triggers for FOG (1). Apart from episodes of FOG, persons with PD and FOG (PD-FOG) display continuous gait abnormalities such as increased stride variability (5).

External cues (i.e. transverse bars on the floor or walking at the rhythm of a metronome) are well-known strategies to reduce FOG (6) and improve speed, cadence (7-9) and stride length variability (10-12), with an additional increase in step length for visual cues (7-9). Despite their potential effectiveness, the use of cues is limited by practical constraints such as a lack of portability and hindrance of bystanders (e.g. housemates). Smart glasses, also called augmented reality (AR) glasses, have the potential to provide portable, personalized cues in an augmented reality overlay on top of a user's visual field. Smart glasses have been welcomed as an assistive technology to facilitate daily living by a majority of respondents in a user requirement survey amongst persons with PD (13, 14).

A previous study compared the effects of rhythmic flashes, a visual flow and a static placebo delivered by virtual reality glasses with transverse lines on the floor on FOG and gait parameters. This study found a deterioration of gait with rhythmic flashes, a marginal improvement only of task completion time with the virtual visual flow and the largest improvement of FOG and gait parameters with transverse lines on the floor (15). In another study, three types of external cues (a metronome, flashing light, and optic flow) delivered via the Google Glass reduced the variability of cadence and stride length, suggesting a more stable gait pattern (12). There was no significant effect on FOG, possibly due to a low overall number of FOG episodes. Some participants disliked the placement of the display in the right upper corner, and instead suggested a binocular projection focally in the visual field. To avoid distraction, it is

important to minimize interference of augmented visual cues with normal visual perception. Therefore, visual cues should be displayed as if they are part of the environment, e.g. augmented bars that are displayed as if they are placed on the floor. This demands that the position and size of the augmented cues are updated in real-time, depending on the position and orientation of the head and the walking speed. Also, it requires the smart glasses to have a sufficiently wide field of view. In addition, to enable users to adjust their steps to augmented visual cues, the augmented cues should start close to the user's body. Furthermore, previous reports (16, 17) suggested that three-dimensional (3D) cues might be more effective in reducing FOG than two-dimensional cues, as were used in previous studies (12, 15). Equally spaced transverse bars on the floor as well as a staircase, either real or as painted optical illusion (17), can constitute such 3D cues. Whether the presentation of transverse bars and staircases via augmented reality influences FOG and gait still needs to be explored. However, smart glasses with displays that are binocular (to enable 3D cues), tiltable and with a sufficient field of view (to allow for display of the cues close to the user), are not yet commercially available. For this purpose, we developed a prototype of custom-made smart glasses and software to provide 3D transverse bars or a staircase in augmented reality. For augmented visual cues to be useful, they should be at least as effective as commonly applied cueing strategies such as conventional 3D transverse bars on the floor (16) or auditory cueing via a metronome (18). It should be carefully investigated whether wearing smart glasses, even when switched off, interferes with the effects of external cues. Possibly, augmented visual cues might not only affect FOG provoked by spatially demanding situations such as gait initiation, but also those provoked by temporal triggers such as turning while walking. Originally, visual cues were thought to provide spatial information that could aid patients in scaling their movements (18), while auditory cues are considered to provide an external rhythm to which movements can be coupled to in the presence of a disrupted internal rhythm (18-20). Interestingly, moving visual targets have also been shown to improve motor timing in finger tapping tasks in healthy individuals, thereby activating regions in the basal ganglia which are associated with motor control and temporal processing (21, 22). Whether moving visual cues, such as augmented

visual cues updated in real-time, can reduce both spatially and temporally triggered FOG is not yet known. In addition to their effectiveness, user satisfaction should be carefully investigated to assess the usability of 3D augmented visual cues delivered by smart glasses.

The present study investigates the usability of 3D augmented visual cues delivered by smart glasses in comparison to conventional 3D transverse bars on the floor and auditory cueing via a metronome in reducing the occurrence of FOG, the percentage of time spent on FOG, and the variability of stride length and cycle time.

Materials and methods

Participant selection

This study was performed in accordance with the guidelines of the Declaration of Helsinki (1964) and was approved by the medical ethics committee Twente. All subjects provided written informed consent prior to their inclusion in the study. Persons aged over 18 years, with Parkinson's disease according to the UK Brain Bank criteria (23), and subjective presence of FOG (score 1 on question 1 from the New Freezing of Gait Questionnaire (NFOGQ) (24)) more than once per day (score 3 on question 2 from the NFOGQ) were eligible for inclusion. Exclusion criteria were: stroke in the medical history, psychiatric disease interfering with assessment of FOG, severe uncorrected visual or hearing impairments disabling the participant to perceive visual or auditory cues, co-morbidity limiting ambulation, inability to walk unaided, a deep brain stimulator or apomorphine pump, jejunal levodopa gel infusion, and severe cognitive impairments (mini-mental state examination (MMSE) <24 at the moment of inclusion). As in several previous studies(12, 25), participants were tested at the end of their regular dopaminergic medication cycle (i.e. while experiencing the end-of-dose phenomenon), because this closely resembles the real life situation where the most FOG occurs during an OFF state when the dopaminergic medication has been wearing off. Thus, participants were tested at the time when they would normally take their (after-)noon levodopa and were instructed to postpone this levodopa intake until after the walking trials. Prior to testing, the following questionnaires

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were taken: NFOGQ (24), MMSE (26, 27), frontal assessment battery (FAB) (28), Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (29).

Smart glasses system

A prototype of custom-made smart glasses (Cinoptics, Maastricht, the Netherlands) was used to display the augmented cues and was worn throughout the experiment (Figure 1). These binocular smart glasses contained two CE-certified see-through optical color displays (organic light-emitting diodes [OLEDs], with 1280 x 720 pixel resolution, a 60Hz refresh rate, and a diagonal field of view of 45 degrees), which could be tilted up to 30 degrees. The participant's head orientation was measured with an inertial measurement unit (IMU) with a sampling frequency of 160Hz. The displays were mounted in a black frame attached to adjustable head straps, weighting 530 grams altogether. The smart glasses were connected with a Microsoft Surface Pro 4 tablet carried inside a mesh pack worn on the participant's back. In addition, participants wore a MVN Awinda motion capture system (Xsens, Enschede, the Netherlands) for collection of motion data. This system consisted of 17 IMU's with three-dimensional gyroscopes, accelerometers, and magnetometers (60Hz sampling frequency, 30ms latency) attached to the feet (2), lower legs (2), upper legs (2), pelvis (1), hands (2), forearms (2), upper arms (2), sternum (1), shoulders (2) and head (1) with Velcro straps. The sensors were calibrated without the participant wearing the smart glasses (to avoid magnetic disruption of orientation) at the start of the experiment and re-calibrated during the experiment if the sensor orientation was disrupted. The motion data were transmitted via a wireless local area network to a laptop with the MVN studio 4.2.0 software installed, and then to the tablet. Custom-made software on the tablet used the incoming data from the IMU's of the smart glasses and the motion capture system to update the position of the augmented cues displayed by the smart glasses in real time. This resulted in the augmented cues being displayed as if they were placed on the floor.
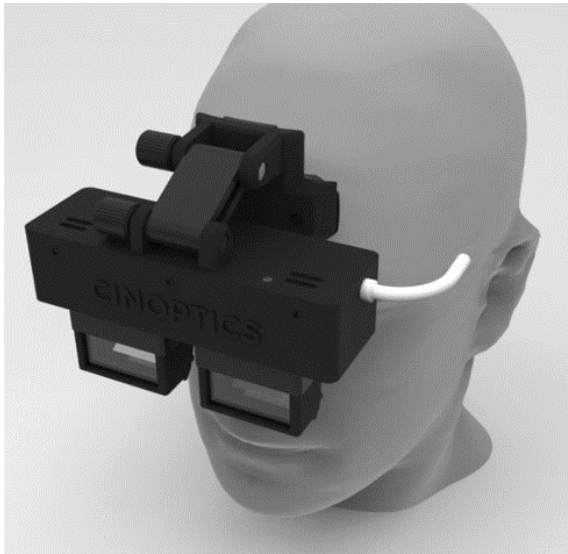
Figure 1. Illustration of the prototype of custom-made smart glasses (Cinoptics, Maastricht, the Netherlands) on a model. The prototype is specifically designed for a large field of view and adjustable angle to allow augmented reality visual cues to be presented as if they are placed on the floor. Binocular see-through displays are mounted in a black frame attached to adjustable head straps (not shown here).

Cues

The following five conditions were tested: 3D augmented transverse bars (AB) (see video 1 for an illustration), 3D augmented staircase (AS) (video 2), equally spaced transverse conventional bars on the floor (CB), auditory cueing via a conventional metronome (CM) and no cues (OFF). The smart glasses were worn during all conditions. The dimensions of the augmented bars were set to match those of the conventional bars, which measured 914mm (width) x 19mm (depth) x 19mm (height) with a distance in between the bars of 40% of the participant's height rounded to the nearest 5cm, based on previous studies (9, 15, 30). The augmented staircase was set to match a real staircase measuring 914mm (width) x 254mm (depth) x 196mm (height). The position of the augmented bars and staircase were adjusted in real time according to the walking speed and head orientation of the participant. The bars in conditions CB and AB, and the staircase in condition AS were all colored white. The

metronome in condition CM was played via speakers at a clearly audible volume, at 110% of a participant's preferred cadence (25, 31-33).

Walking courses

The walking trajectory consisted of a 15m walking track along an empty corridor at the University of Twente, with a passage at 7.5m made-up by two chairs placed 50cm apart (Figure 2). Three different walking courses were performed along this walking trajectory. In the 'walking straight' (-) course, participants walked along the walking trajectory without any additional task. In the 'stop and start' (S) course, pre-recorded voice commands signalled the participants to stop walking at three random distances along the track; they were instructed beforehand to resume walking on their own initiative. In the 'turning' (T) course, participants were signalled by pre-recorded voice commands to make a full 360^0 turn at three random distances along the track. No stop-signals or turn-signals were given in the 'no signal - zone' at the first and last 2 meter of the walking trajectory.

The experiment consisted of 2 sessions separated by a half an hour break. Each session consisted of 5 'blocks' with one condition (AB, AS, CB, CM or OFF) per block. A block included all the walking courses (-, S, T) performed once. Hence, each condition-course combination was performed once per session. In between blocks, participants were offered to rest as long as needed. The order of the conditions (AB, AS, CB, CM, OFF), the courses (-, S, T), and the timing of the 'stop' and 'turn'-signals were balanced by the experiment control software on the laptop. Experiments were performed in a single visit, lasting on average 2.5 to 3 hours.

Prior to the experiment, participants familiarized themselves with the smart glasses, the augmented cues and the conventional bars. Each walking course was explained, shown and practiced until performed correctly. Participants were not instructed in explicit detail on how to handle the cues. After the first session, participants were asked whether they wanted to continue with the second session after the break, or quit (for example because of tiredness).
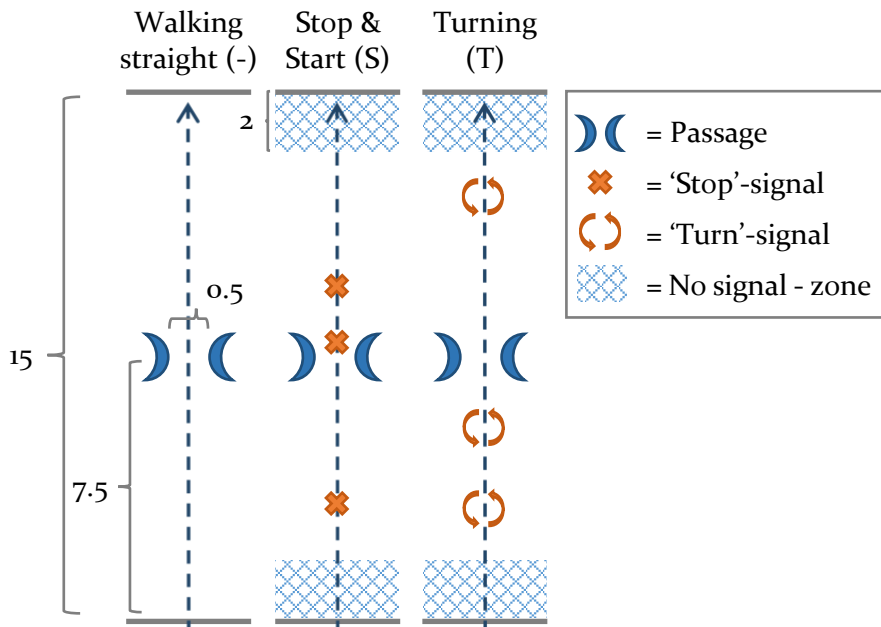
Figure 2. Walking courses
In each of three walking courses, the participant walked across a 15 meters long walking trajectory with a passage at the middle of the trajectory created by two chairs 0.5 meters apart. In the walking straight (-) course, no additional task was performed. In the 'stop and start' (S) course, pre-recorded voice commands signaled the participants to stop walking at three random distances along the track. Participants were instructed to resume walking on their own initiative. In the 'turning' (T) course, participants were signaled by pre-recorded voice commands to make a full 360^0 turn at three random distances along the track. No stop-signals or turn-signals were given in the 'no signal - zone' at the first and last 2 meter of the walking trajectory. All measures in Figure 2 are given in meters.

User interview
A semi-open structured interview was performed after the walking trials to assess participants' experience with the smart glasses and cues (Supplementary table 1). This interview encompassed questions and

statements regarding the use of technical devices, usefulness of the four different cues (AB, AS, CB, CM), ease of use and learning, satisfaction with the glasses and cues, preferences, and suggestions regarding the glasses and cues. Participants were asked to rate on a 5-point Likert scale (1 representing 'totally disagree', 5 'totally agree') how much they agreed with the statements, and were invited to elaborate on their answer. For question 7, which asked for cueing condition preferences, the condition preferred the most (question 7.1) was assigned 5 'preference points', the second most preferred condition (question 7.2) 4 preference points, and so on up to the least preferred condition (question 7.5). Preference points were summed per condition.

Data analysis

A video recorder at each end of the walking trajectory recorded all trials on video for *post hoc* analysis of FOG. In accordance with the current working definition, FOG was defined as 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk'(1). Two independent raters (SJ, JN) were blinded for the condition (except for the conventional bars) and scored the videos for number and duration of FOG per trial. Discrepant ratings were discussed until consensus was reached. Motion data from the Awinda motion capture system was wirelessly transmitted to MVN studio version 4.2.0. Orientation and position data, calculated by MVN studio, together with raw accelerometer and gyroscope data were exported to MATLAB R2014b (Mathworks, Inc., Natick, MA, USA) for the offline calculation of gait parameters as previously described(12).

Primary performance measures were the number of FOG episodes, the percentage of time spent on FOG, and the variability (represented by the standard deviation) of the stride length and cycle time. Secondary performance measures were the stride length, cycle time, cadence and speed.

All statistical tests were performed in IBM SPSS version 24. An alpha of 0.05 was applied for all two-sided tests. Normality of distributions was tested with the Shapiro-Wilk test. Central tendency and statistical dispersion are given as the mean and standard deviation (SD) if distributions were normally distributed, and otherwise as the median and interquartile range (IQR). The

number of FOG episodes and the percentage of time spent on FOG (calculated as the cumulative duration of FOG divided by the summed duration of trials multiplied with 100, per individual and per condition) were compared in participants who experienced at least one FOG episode throughout the experiment. Sub-analyses were performed for FOG episodes occurring during turning, and during non-turning events. In addition, sub-analyses were performed for the number of FOG episodes and the percentage of time spent on FOG in the participants who experienced the most FOG episodes (defined as a total number of FOG episodes above the median number of FOG episodes in all participants with at least one FOG episode).

The mean and standard deviation of the step length and of the time to complete one gait cycle (cycle time), cadence and walking speed were analysed exclusively for the 'walking straight' courses, in all participants. Kinematic parameters were calculated as the median values per participant, per condition, and then compared across participants for each cueing condition. A one-way repeated measures ANOVA was applied in the case of normally distributed data. If the assumption of sphericity, as assessed by Mauchly's test of sphericity, was violated, a Greenhous-Geisser correction was applied. The non-parametric Friedman test was used in case of non-normality. All *post hoc* pairwise comparisons were performed with a Bonferroni correction for multiple comparisons.

From the exit interview, median scores are reported for questions answered on a 5-point Likert scale. Questions with open answers and elaborations on the closed questions were qualitatively assessed.

Results

Clinical characteristics of the participants are summarized in Table 1. All 25 participants completed the first session. Five participants did not perform the second session because of physical tiredness, resulting in 20 participants who completed both sessions. The results of the statistical tests on FOG and gait parameters are summarized in Table 2.

Table 1 Clinical characteristics of the participants (N = 25)

	Median	Range
Age (years)	72	65 – 79
Gender (% male)	76	
Height (cm)	171	159 – 189
Body mass index (kg/m²)	27.1	21.7 – 37.2
Disease duration (years)	11	3 – 20
Years since FOG (years)	2	0.25 – 12
Daily levodopa dosage (mg/day)	750	0 – 1200
UPDRS-part III	34	10 – 61
UPDRS-PIGD	6	2 – 12
Hoehn and Yahr	2	2 – 3
MMSE	28	19 – 30
N-FOGQ	18	8 – 28
FAB	14	5 – 26

'FOG' = Freezing of Gait. 'UPDRS-part III' = Unified Parkinson's Disease Rating Scale part III: Motor examination. 'UPDRS-PIGD' = Unified Parkinson's Disease Rating Scale – Postural instability and gait disorder (question 3.9 up to 3.13 from UPDRS-part III). 'MMSE' = mini-mental state examination. 'N-FOGQ' = New Freezing of Gait Questionnaire. 'FAB' = Frontal Assessment Battery. All questionnaires, including the UPDRS, were rated while participants were end-of-dose.

Freezing of gait

There was a high degree of consensus between raters (SJ and JN) on the rating of number (r_s(23) = 0.979, p < 0.0005) and total duration of FOG episodes (r_s(23) = 0.974, p < 0.0005) per participant. In 19 out of 25 participants, at least one FOG episode occurred during the experiment, with a total of 300 FOG episodes for all persons together. Of these, 18 participants experienced a total

of 224 FOG episodes during turning, and 8 participants experienced FOG during walking straight (20 episodes), gait initiation (18 episodes), passing the passage (21 episodes), or upon coming to a standstill (17 episodes). Only participants in whom at least one FOG episode occurred (N = 19) were included in the analysis of the effect of cues on FOG. The number of FOG episodes (Figure 3a) and the percentage of time spent on FOG (Figure 3b) were non-normally distributed, hence the Friedman test was used. Although there was a statistically significant difference amongst the various cues for number of FOG episodes, pairwise comparisons failed to show a significant difference. There was no statistically significant difference in the percentage of time spent on FOG amongst the different cues. Results were similar when performing a sub-analysis for FOG episodes occurring during turning (representing temporally triggered FOG), and during non-turning events (representing spatially triggered FOG). Sub-analyses among participants with the greatest number of FOG episodes (N = 10) again showed no statistically significant difference in number of FOG episodes nor in the percentage of time spent on FOG across the five conditions.

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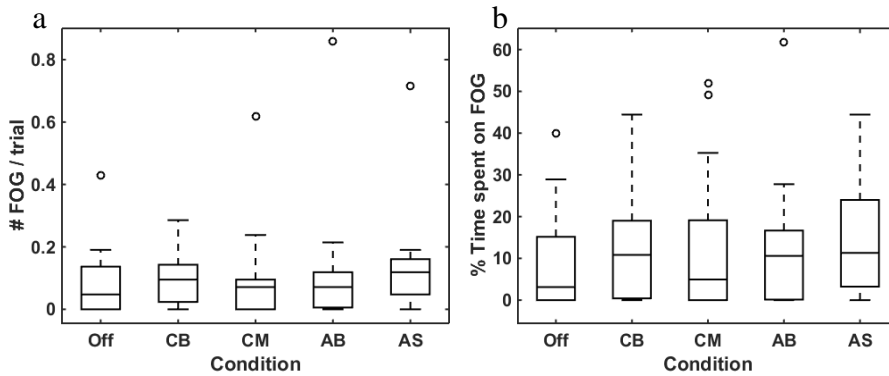
Figure 3. Effects of conditions on FOG occurrence

Boxplots visualizing the effect of the five conditions on mean number of FOG episodes per trial (a) and percentage of time spent on FOG (b) for each condition in participants who experienced more than one FOG episode throughout the experiment (N = 19). 'Off' = smart glasses worn but switched off; 'CB' = conventional bars; 'CM' = conventional metronome; 'AB' = augmented bars; 'AS' = augmented staircase.

Table 2 FOG and gait parameters per condition

PARAMETER	OFF	CB	CONDITION CM	AB	AS	p-VALUE
FOG PARAMETERS [1]						
Mean number of FOG per trial	0.08 (0.11)	0.10 (0.08)	0.09 (0.14)	0.11 (0.19)	0.13 (0.15)	0.042†,A
% time spent on FOG	9.05 (12.11)	12.73 (13.08)	12.34 (16.86)	12.41 (15.28)	15.56 (13.68)	0.090†
GAIT PARAMETERS [2]						
Stride length variability	0.17 (0.12)	**0.21 (0.10)**[B]	0.17 (0.13)	0.16 (0.14)	**0.15 (0.07)**[B]	0.001*
Cycle time variability	0.24 (0.06)	0.31 (0.27)	0.24 (0.12)	0.24 (0.12)	0.21 (0.13)	0.117*
Stride length (m)	0.92 (0.35)	**1.19 (0.57)**[C,D]	0.94 (0.37)	**0.93 (0.32)**[C]	**0.86 (0.37)**[D]	0.001*
Cycle time (sec)	**1.15 (0.16)**[E]	**1.60 (0.33)**[E,F,G,H]	**1.15 (0.16)**[F]	**1.18 (0.25)**[G]	**1.18 (0.16)**[H]	< 0.0005†
Cadence (steps/min)	**102.76 (13.88)**[I]	**74.41 (15.83)**[I,J,K,L]	**102.81 (14.38)**[J]	**100.40 (19.63)**[K]	**99.85 (13.41)**[L]	< 0.0005†
Speed (m/sec)	**0.83 (0.41)**[M]	**0.72 (0.44)**[M,N]	**0.84 (0.42)**[N]	0.78 (0.34)	0.75 (0.40)	0.001†

[1] FOG parameters in mean (standard deviation), in participants with more than one FOG episode throughout the experiment (N = 19); all walking courses. [2] Gait parameters in median (interquartile range), in all participants (N = 25); during 'straight walking' courses. OFF: smart glasses switched OFF; CB: conventional bars; CM: conventional metronome; AB: augmented bars; AS: augmented staircase.

p-values for within group differences are calculated with a one-way repeated measures ANOVA (*) or Friedman test (†). Statistically significant differences (adjusted $p < 0.05$, two-sided tests) between pairs of cues are printed bold, with the test statistic and p-value given in the legend. [A] upon post hoc pairwise comparisons no statistically significant differences between cue-pairs. [B] χ^2 2.048, $p < 0.0005$. [C] χ^2 1.571, $p = 0.013$. [D] χ^2 1.762, $p = 0.003$. [E] $p < 0.0005$, 95% CI difference CB-OFF 0.30 to 0.55. [F] $p < 0.0005$, 95% CI difference CB-CM 0.31 to 0.54 [G] $p < 0.0005$, 95% CI difference CB-AB 0.26 to 0.49. [H] $p < 0.0005$, 95% CI difference CB- AS 0.27 to 0.52. [I] $p < 0.0005$, 95% CI difference CB-OFF -32.42 to -18.56. [J] $p < 0.0005$, 95% CI difference CB - CM -31.88 to -20.07). [K] $p < 0.0005$, 95% CI difference CB - AB -30.09 to -15.19) . [L] $p < 0.0005$, 95% CI difference CB - AS -30.99 to -17.02). [M] $p = 0.010$, 95% CI difference CB-OFF -0.23 to -0.02. [N] $p = 0.007$, 95% CI difference CB-CM -0.22 to -0.03.

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Gait variability

The median stride length variability was statistically significant higher for the conventional bars compared to the augmented staircase (Figure 4a and Table 2). There was no statistically significant difference in cycle time variability amongst the various conditions (Figure 4b; Table 2).

Stride length and cycle time

The stride length was statistically significant larger for the conservative bars compared to the augmented bars and the augmented staircase (Figure 4c; Table 2). The median cycle time showed one outlier for the no cue-condition; exclusion of the outlier did not change the results, hence the outlier was included in the analysis. The assumption of sphericity was violated ($\chi^2(9)$ =28.564, p = 0.001) and therefore a Greenhous-Geisser correction was applied (ε = 0.555). The median cycle time was statistically significant higher for the conventional bars when compared to the no cue-condition, the conventional metronome, the augmented bars and the augmented staircase (Figure 4d; Table 2).

Cadence and speed

Cadence showed no outliers and the assumption of sphericity was not violated ($\chi2(9)$ =13.979, p = 0.124). The median cadence was lower for the conventional bars compared to the no cue-condition, the conventional metronome, the augmented bars and the augmented staircase (Figure 4e; Table 2). For speed, the assumption of sphericity was violated ($\chi2(9)$ =24,325, p = 0.004), hence a Greenhous-Geisser correction was applied (ε = 0.594). The median speed was lower for the conventional bars compared with the no cue-condition and the conventional metronome (Figure 4f and Table 2).
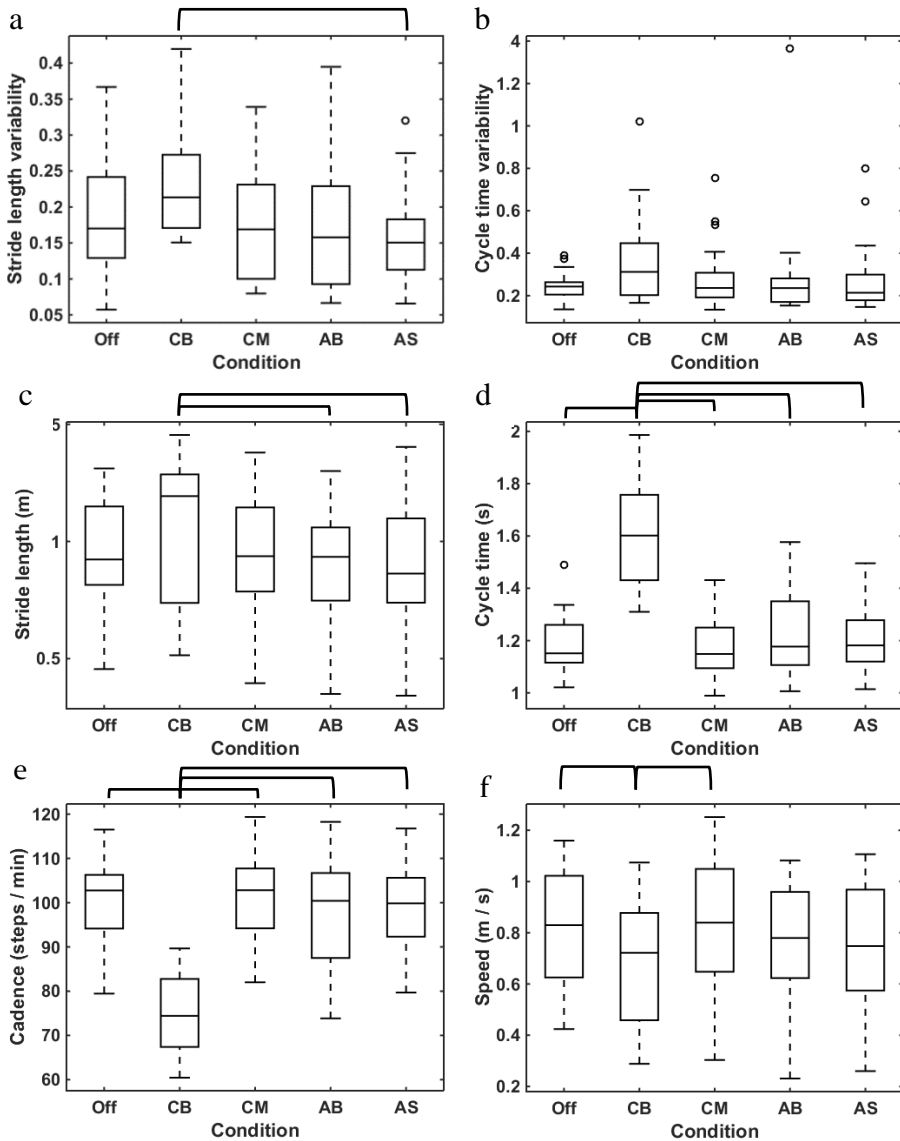
Figure 4 Effects of conditions on gait parameters.
Boxplots visualizing the effects of the five conditions on stride length variability (**a**), cycle time variability (**b**), mean stride length (**c**), mean cycle time (**d**), cadence (**e**) and speed (**f**) calculated in straight-walking trials in all participants (N = 25). The brackets indicate statistically significant differences in the parameters concerned between conditions ($p < 0.05$). The statistical test values are given in Table 2.

User experience

Overall, the conventional metronome was preferred the most (99 preference points), followed by the conventional bars (80 preference points), augmented bars (77 preference points), no cues (61 preference points) and augmented staircase (58 preference points). Participants indicated they could walk better with cues (AB/AS/CB/CM 4), that all cues except the augmented staircase made walking easier (AS 3; AB/CB/CM 4), and that they considered all cues except the augmented bars useful (AB 3; AS/CB/CM 4). The metronome was considered the most well-suited cue to provide more control over daily life activities (CM 4; AB/AS/CB 3) and met participants' needs (CM 4; AB 2; AS/CB 3) and expectations (CM 4; AB/AS 3; CB 2) the most. The augmented bars and conventional bars were considered less distracting than the augmented staircase and conventional metronome (AB/CB 4; AS/CM 3). Ease of use, usability and willingness to use the smart glasses in everyday life were rated low (2). The use of smart glasses did not require additional effort (3) and walking with smart glasses was considered easy to learn (4). Participants suggested to improve the comfort, aesthetics, usability, field of view and stability of the smart glasses on the head and to reduce their weight and size. With regard to the augmented cues, three participants suggested to experiment with softer colours than the current white, and three participants suggested to broaden the augmented cues, and one participant wished for footsteps on the augmented staircase.

Discussion

The present study investigated the usability of 3D augmented visual cues delivered by smart glasses, conventional 3D bars on the floor, a metronome or no cues on the occurrence of FOG, the percentage of time spent on FOG, the (variability of) stride length and cycle time, cadence and speed. Note that the smart glasses were worn during all conditions, but only switched on for the augmented bars and staircase. Neither the augmented bars and staircase, the conventional bars on the floor, nor the metronome reduced the number of FOG episodes or the percentage of time spent on FOG. Results were similar in the subset of FOG episodes occurring during spatially demanding situations, when the FOG episodes triggered by turning were excluded. The conventional

bars caused an increase in stride length, cycle time and stride length variability, and a decrease in cadence and speed. There was no effect of the other cues on gait parameters.

That the conventional bars on the floor and the metronome failed to reduce FOG contradicts studies reporting a reduction in FOG by visual (16, 34) or auditory (34, 35) cues. The influences of conventional bars on gait parameters could be attributable to the distance between the bars depending on the participant's height (leading to larger and slower steps if the distances between the bars were larger than a participants' preferred uncued step length), and the observation that participants varied the number of steps in between two bars, increasing stride length variability. That other cues did not alter gait parameters does not correspond to earlier studies (7, 10, 11).

We propose several possible explanations for the lack of effects of cues on FOG and gait parameters. First, participants were not used to walking with smart glasses, and this novel experience, together with their experience of the smart glasses being quite heavy and uncomfortable, might have caused distractions. It is well-recognized that dividing attention is impaired in PD-FOG (36), and FOG severity has been correlated with difficulties in switching attention (37). Dual tasks, which also require switching or dividing attention, are known to deteriorate FOG (38), and to counteract the FOG-alleviating effects of visual cues (39). Considering that FOG occurrence did not differ amongst conditions (including with the smart glasses switched off), the smart glasses themselves rather than the cues might have caused distraction. This may have cancelled out the FOG-ameliorating effect of cues. With regard to gait parameters, dual tasks are known to decrease step length, walking speed (39), and increase cadence (38) and step length variability (39) in PD-FOG, effects which are undone in the presence of visual cues (39). Because a condition without smart glasses was not included, we cannot rule out that the smart glasses induced distraction, similar to a dual task, altering these gait parameters. However, the previous observation that dual task-induced gait alterations could be reversed by visual cues (39) was not found in our study. The rather 'bulky' design of this prototype of smart glasses was due to technical constraints raised by the requirements to deliver 3D augmented cues as if placed in the real

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environment. Second, the duration of the experiment might have been insufficient for participants to familiarize themselves with the smart glasses and cues. Indeed, in former studies, immediate effects of cues were variable, while longer periods of cueing training were thought to be more effective (18). Third, the frame of the smart glasses blocked part of the peripheral visual field. This might have reduced the visual feedback which persons with PD-FOG are more reliant on due to impaired propriocepsis (40-43). A previous study showed that blocking the view of the lower limbs caused an increase in FOG, which visual cues did not prevent (39). Hence, the frame of the smart glasses might have reduced visual sensory feedback, thereby increasing FOG occurrence in all conditions, which was not reversed by visual cues. In addition, blockage of the visual field has previously shown to decrease step length, velocity and cadence, which was reversible with visual cues in one (39), but not in another study (41). Such difference in gait parameters between visually cued and un-cued conditions could not be confirmed in our study. Fourth, the augmented visual cues as well as the conventional bars were all perceived in the central visual field. It has been suggested that the integration of information from the central and peripheral visual fields is important for the perception of self-movement (44) and that typically a stationary centre with a moving periphery induces a sense of self-movement. Moving visual cues in the central visual field, such as in our experiment, constitute the opposite situation. This might influence the sense of self-motion, thereby affecting motor planning and potentially contributing to the occurrence of FOG (45). However, currently used visual cues such as bars on the floor or laser lights (46-48) are predominantly presented in the central visual field, while an enhanced peripheral optic flow delivered via Google Glass did not reduce FOG (12). Fifth, dopaminergic medication levels at the end-of-dose might have interfered with the effects of cueing. Studies finding no effects of cues on FOG and gait parameters were predominantly performed in the ON state (15, 49-52). However, rather than that medication interferes with the effects of cues, these studies might have been underpowered to find effects of cues on gait parameters that (due to the symptomatic effect of medication) were less severely disturbed than in the OFF state. Positive effects of cues have been reported by studies performed in the OFF (15, 34, 35, 52, 53), ON (6, 10) as well

as the end-of-dose state (25). The role of medication state on response to cues remains to be established.

A limitation of this study is the absence of a control condition without smart glasses and cues, which would have allowed to distinguish distraction by the smart glasses, as discussed above. Furthermore, 224 out of 300 FOG episodes occurred during turning, which might be more receptive to temporal than spatial cues. The remaining 76 non-turn FOG episodes, which could potentially be more sensitive to visual cues, might have been too few to find a statistically significant effect.

In conclusion, three-dimensional augmented visual cues delivered by customized smart glasses did not improve FOG nor gait stability in persons with PD-FOG. Adjustments to smart glasses are prerequisite to turn them into effective cueing devices, amongst others by a more light-weight, comfortable and user friendly design, a wider field of view and less interference with sensory visual feedback. Future research should investigate whether, and through which mechanisms, 3D cues are more effective than 2D cues; whether novel cues affect FOG provoked by spatial as well as temporal triggers; and whether visual cues should be presented in the central or peripheral visual field. Furthermore, it is of particular interest whether a larger effect of augmented visual cues can be obtained with a longer habituation period, or when cues are provided 'on demand'. Ideally, future studies should include healthy control individuals to assess whether cues affect gait parameters differently in persons with PD and healthy controls. To avoid a 'trial-and-error'-based development of new cueing devices, it is important to deepen our insights into the characteristics of effective cues, requirements for new cueing devices, and the neuronal mechanisms underlying externally cued (freezing of) gait.

Supplementary material

The supplementary videos for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00279/full#supplementary-material.

Legend Supplementary Video 1

Illustration of the simulation of 3D transverse bars displayed in augmented reality perceived through the smart glasses. The upper half of the screen represents a top view of the walking direction of the user; here walking forward, turning 90 degrees to the left and resuming to walk forward. The lower half of the screen represents the augmented reality display. White 3D transverse bars are updated in real time upon movement of the user. The black area represents the part of the display where no augmented reality images are being displayed, and the 'real environment' is transmitted to be perceived by the user.

Legend Supplementary Video 2

Illustration of the simulation of a 3D staircase displayed in augmented reality perceived through the smart glasses. The upper half of the screen represents a top view of the walking direction of the user; here walking forward, turning 90 degrees to the left and resuming to walk forward. The lower half of the screen represents the augmented reality display. A white 3D staircase is updated in real time upon movement of the user. The black area represents the part of the display where no augmented reality images are being displayed, and the 'real environment' is transmitted to be perceived by the user.

Supplementary table 1

1	Medical history	
1.1	"When did you first experience symptoms of Parkinson's disease?"	Open
1.2	"Which were those first symptoms?"	Open
1.3	"When did you develop freezing of gait?"	Open
1.4	"Do you use cues to reduce freezing of gait?"	Yes / No
1.5	If 'yes' to question 1.4: "which cues?"	Open
2	Use of technical devices	
2.1	"Do you use a mobile phone (not a smartphone)?"	Yes / No
2.2	"Do you use a smartphone?"	Yes / No
2.3	"Do you use a tablet or iPad?"	Yes / No
2.4	"Do you use a computer or laptop?"	Yes / No
3	Usefulness of cues	

3.1	"The augmented bars via the smart glasses [...]	
3.1.1	[...] improved my walking."	Likert scale
3.1.2	[...] are useful."	Likert scale
3.1.3	[...] could give me more control over daily life activities."	Likert scale
3.1.4	[...] make walking easier."	Likert scale
3.1.5	[...] fulfil my needs."	Likert scale
3.1.6	[...] do everything I expected it to do."	Likert scale
3.1.7	[...] are NOT distracting."	Likert scale
3.2	"The bars on the floor [...]	
3.2.1	[...] improved my walking."	Likert scale
3.2.2	[...] are useful."	Likert scale
3.2.3	[...] could give me more control over daily life activities."	Likert scale
3.2.4	[...] make walking easier."	Likert scale
3.2.5	[...] fulfil my needs."	Likert scale
3.2.6	[...] do everything I expected it to do."	Likert scale
3.2.7	[...] are NOT distracting."	Likert scale
3.3	"The augmented staircase via the smart glasses [...]	
3.3.1	[...] improved my walking."	Likert scale
3.3.2	[...] are useful."	Likert scale
3.3.3	[...] could give me more control over daily life activities."	Likert scale
3.3.4	[...] make walking easier."	Likert scale
3.3.5	[...] fulfil my needs."	Likert scale
3.3.6	[...] do everything I expected it to do."	Likert scale
3.3.7	[...] are NOT distracting."	Likert scale
3.4	"The metronome [...]	
3.4.1	[...] improved my walking."	Likert scale
3.4.2	[...] is useful."	Likert scale
3.4.3	[...] could give me more control over daily life activities."	Likert scale
3.4.4	[...] makes walking easier."	Likert scale
3.4.5	[...] fulfils my needs."	Likert scale

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3.4.6	[...] does everything I expected it to do."	Likert scale
3.4.7	[...] was NOT distracting."	Likert scale
4.1	Ease of use	
4.1	"The smart glasses are easy."	Likert scale
4.2	"The smart glasses are user friendly."	Likert scale
4.3	"Using the smart glasses requires little effort."	Likert scale
4.4	"I would like to use the smart glasses regularly."	Likert scale
4.5a	"I would like to use the smart glasses on certain occasions."	Likert scale
4.5b	(if score ≥ 4 on question 4.5a) On what occasions?	Open
4.6	"The cues via the smart glasses were easily visible."	Likert scale
5	Ease of learning	
5.1	"I learned to walk with the smart glasses quickly."	Likert scale
5.2	"It is easy to learn to walk with the smart glasses."	Likert scale
6	Satisfaction	
6.1	"I am satisfied with the smart glasses."	Likert scale
6.2	"I would recommend the glasses to a friend."	Likert scale
6.3	"It is fun to use the smart glasses."	Likert scale
6.4	"The smart glasses work the way I want them to work."	Likert scale
6.5	"The smart glasses are wonderful."	Likert scale
6.6	"I feel that I need the smart glasses."	Likert scale
6.7	"The smart glasses are pleasant to use."	Likert scale
6.8	"If I could take the smart glasses home, I would do so."	Likert scale
7	Preferences	
7.1	"You have walked with the smart glasses with the augmented bars and staircase, with the bars on the floor, with the metronome and without cues. Which cue did you prefer most?"	Likert scale
7.2	"Which cue did you prefer second?"	1 – 5
7.3	"Which cue did you prefer third?"	1 – 5
7.4	"Which cue did you prefer fourth?"	1 – 5
7.5	"Which cue did you prefer fifth, the least?"	1 – 5

7.6	"What adjustments to the augmented bars do you suggest?"	Open
7.7	"What adjustments to the augmented staircase do you suggest?"	Open
7.8	"What adjustments to the smart glasses do you suggest?"	Open
7.9	"Do you have remarks regarding the smart glasses or cues which have not yet been discussed?"	Open

Questions and statements listed here are translated from Dutch. The Dutch questions and statements were read out to participants in a neutral voice. The last column lists the answer types. 'Open': verbalization of the answer without being offered a choice of answers. 'Yes / No': choice between 'yes' and 'no'. 'Likert scale': agreement with the statement on a five-point Likert Scale, ranging from 1 ('totally disagree') to 5 ('totally agree'); participants were welcomed to elaborate on their answer.

Abbreviation list

PD: Parkinson's Disease; FOG: Freezing of gait; OFF: smart glasses switched OFF; CB: conventional bars; CM: conventional metronome; AB: augmented bars; AS: augmented staircase.

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CHAPTER 7

EFFECTS OF AUGMENTED REALITY GLASSES ON FOG AND CUEING EFFECTS

THE BENEFICIAL EFFECTS OF VISUAL CUES ARE RETAINED
WHEN AUGMENTED REALITY GLASSES ARE WORN

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External cues, such as transverse bars on the floor or the beat of a metronome, can alleviate freezing of gait (FOG) in persons with Parkinson's disease (PD) (1). We previously investigated the effects of augmented reality (AR) visual cues on FOG and hypokinetic gait in persons with PD but found no improvements (2, 3). Surprisingly, conventional cues, i.e. real transverse bars on the floor and the beat of a metronome, neither afforded beneficial effects while persons wore the AR glasses. One possible explanation is that the rather bulky AR glasses (that were worn throughout the experiment) in effect caused a 'dual task' effect and hence inadvertently diverted the participants' attention away from the walking task. Dual tasks are known to deteriorate FOG in PD patients. If wearing AR glasses indeed deteriorates FOG, this might annihilate the beneficial effects of both AR and conventional cues. An alternative explanation could be that the participants in these studies were not responsive to cues in general, as this was not a selection criterion.

We hypothesized that wearing AR glasses could have two negative effects: 1) eliciting or worsening FOG; and (2) annihilating the effects of conventional cues. Additionally, we hypothesized that AR cues could alleviate FOG in a cueing-responsive patient. To test these hypotheses, we tested one person with PD with an established clear response to conventional cues under different cueing conditions. This person was examined here with and without wearing AR glasses. The patient was a 63-years old man who was diagnosed with PD 17 years earlier, and who had experienced FOG for 16 years. He had no cognitive impairments and no relevant comorbidities. His FOG partially improved with dopaminergic medication (levodopa equivalent daily dose 2130 mg), but remained bothersome nevertheless. He reported no beneficial or negative effects of bilateral deep brain stimulation of the subthalamic nucleus on his FOG. He successfully used a wide variety of cueing strategies, such as auditory and haptic metronomes, bars and lines on the floor, stepping over a broom, and kicking against a small box on the floor.

The experiment was conducted in a medication OFF state, >12 hours after the last intake of dopaminergic medication. The deep brain stimulator was left switched on. The patient traversed a doorway four times under each of the following conditions: (1) no AR glasses worn, no cues applied ('Control'); (2)

the AR glasses worn but switched off ('SG OFF'); (3) AR three-dimensional bars displayed through the AR glasses ('SG AR'); (4) real transverse bars on the floor, no AR glasses worn ('Real bars'); (5) real transverse bars on the floor while wearing AR glasses switched off ('SG real bars'); (6) stepping over a hand-held broom, no AR glasses worn ('Broom'); and (7) kicking against a small box on the floor, no AR glasses worn ('Box'). The AR glasses used were the Microsoft Hololens (2017, developer version, Microsoft). FOG was annotated from video recordings by two independent experienced raters. The percent time of the trial spent on freezing was compared amongst the different cueing conditions with paired t-tests.

The real bars, broom and box caused a remarkable and significant improvement in percent time frozen compared to the control condition, confirming that this person was particularly responsive to visual cues (figure 1 & supplementary video 1). Wearing AR glasses did not increase the percent time frozen compared to the control condition, although the percent time frozen was already high (94%) in the control condition. The positive effect of real bars on the percent time frozen was not negatively affected by wearing the AR glasses. The AR visual cues did not improve FOG (Figure 1 & supplementary video 1). This might have been due to the limited field of view of the AR glasses, disrupting the perception of being able to step over the AR bars. Alternatively, the patient's awareness that the AR cues were 'not real' might have affected the cues' potency.

From this single patient study we conclude that wearing AR glasses does not worsen FOG nor affect the beneficial effects of conventional cues, and that AR visual cues do not improve FOG even in a cueing-responsive patient. Whether these conclusions can be extended to other patients requires further study in a larger cohort. We recommend future studies involving cueing through AR glasses to include control conditions without AR glasses.
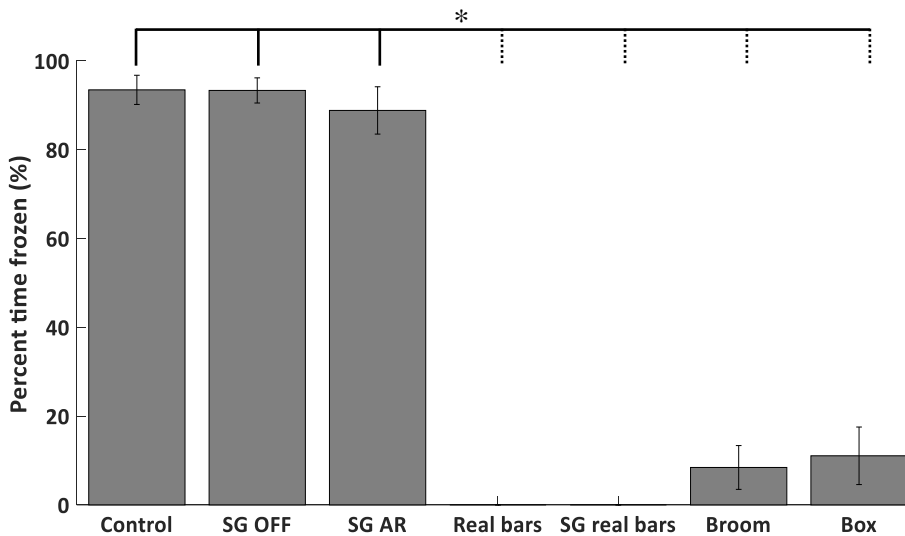
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Figure 1. Percent time frozen (PTF) under different cueing conditions. Bar plot with error bars representing the standard error of the mean. Each of the three conditions on the left (solid vertical bar) shows a statistically significant difference from each of the four conditions on the right (dashed vertical bar) (p<0.05). 'Control' = no cues, no AR glasses; 'SG OFF' = AR glasses worn and switched off; 'SG AR' = AR bars displayed through AR glasses; 'Real bars' = real transverse bars on the floor, no AR glasses worn; 'SG real bars' = real transverse bars on the floor, AR glasses worn but switched off; 'Broom' = stepping over a hand-held broom, no AR glasses worn; 'Box' = kicking against a small box on the floor, no AR glasses worn.

Supplementary material

Supplementary video material is accessible through http://hdl.handle.net/11633/aacy3qb4.

Legend supplementary video 1

First-person view of the augmented reality three-dimensional transverse bars displayed through the augmented reality glasses. The wearer first moves the head up, looking ahead of the walking track (00:00 – 00:03 sec), and then back to just ahead of the feet (00:03 – 00:07 sec). Next, the wearer walks forward

along the walking track, thereby crossing the augmented reality bars (00:07 – 00:19 sec), performs a half turn, and walks back across the same path (00:23 – 00:30 sec).

Of note: the floor in this demo is different from the floor in the patient measurement. In the patient measurement, there was a carpet with irregular small dots in the room, and a plain grey linoleum floor in the hallway.

Legend supplementary video 2

Videos of trials in the experiment under the various conditions: 'Control' (no cues, no AR glasses) at 0:00 – 00:53 sec. 'SG OFF' (AR glasses worn and switched off) at 00:54 – 02:20 sec. 'SG AR' (AR bars displayed through AR glasses) at 02:21 – 05:36 sec. 'Real bars' (real transverse bars on the floor. no AR glasses worn) at 05:36 – 05:42 sec. 'SG real bars' (real transverse bars on the floor, AR glasses worn but switched off) at 05:42-05:48 sec. 'Broom' (stepping over a hand-held broom, no AR glasses worn) at 05:49 – 05:55 sec. 'Box' (kicking against a small box on the floor, no AR glasses worn) at 05:56 – 06:14 sec.

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CHAPTER 8

AUGMENTED REALITY VISUAL CUES TO SUPPORT TURNING

THE EFFECTS OF AUGMENTED REALITY VISUAL CUES ON TURNING IN PLACE IN PARKINSON'S DISEASE PATIENTS WITH FREEZING OF GAIT

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Abstract

Background: Turning in place is particularly bothersome for patients with Parkinson's disease (PD) experiencing freezing of gait (FOG). Cues designed to enforce goal-directed turning are not yet available. Here, we aimed to assess whether augmented reality (AR) visual cues could improve FOG and turning in place in PD patients with FOG.

Methods: Sixteen PD patients with FOG performed a series of 180 degree turns under an experimental condition with AR visual cues displayed through a HoloLens, and two control conditions (one active, consisting of auditory cues; and one without any cues). FOG episodes were annotated by two independent raters from video recordings. Motion data were measured with 17 inertial measurement units for calculating axial kinematics, and scaling and timing of turning.

Results: AR visual cues did not reduce the percent time frozen (p 0.73), nor the number (p 0.73) and duration (p 0.78) of FOG episodes compared to the control condition without cues. All FOG parameters were higher with AR visual cues than with auditory cues (percent time frozen (p 0.01), number (p 0.02) and duration (p 0.007) of FOG episodes). The AR visual cues did reduce the peak angular velocity (visual vs. uncued p 0.03; visual vs. auditory p 0.02) and step height (visual vs. uncued p 0.02; visual vs. auditory p 0.007), and increased the step height coefficient of variation (visual vs. uncued p 0.04; visual vs. auditory p 0.01) and time to maximum head-pelvis separation (visual vs. uncued p 0.02; visual vs. auditory p 0.005), compared to both control conditions.

Conclusions: The AR visual cues in this study did not reduce FOG, and worsened some measures of axial kinematics, and turn scaling and timing. Stimulating goal-directed turning might, by itself, be insufficient to reduce FOG and improve turning performance.

Background

Turning in place is an inevitable part of daily life mobility which can be particularly bothersome to patients with Parkinson's disease (PD). This is especially true for those patients who experience freezing of gait (FOG), a disturbing motor symptom defined as a 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' (1). Turning is the most common trigger to elicit FOG (2, 3). Both FOG and turns increase the risks of falling and fall-related injuries (4, 5).

Compared to healthy controls, PD patients perform turns more slowly (6-8), with a wider turning arc (8), shorter step length (8, 9), higher step count (6, 10), stronger coupling between head and trunk rotation (i.e. turning 'en bloc') (10), and less medial shifting of the centre of mass (COM) (11). In PD patients with FOG, turn time, cadence, and head-trunk coupling are increased more than in patients without FOG (12, 13). The observation that the head-pelvis sequence (meaning that rotation of the head precedes the trunk) is delayed and reduced - or even absent - in trials with FOG (14) suggests a, not necessarily causal, relationship between head-trunk coupling and FOG. Furthermore, prior to a FOG episode, the COM deviation towards the inner leg is reduced compared to uninterrupted turning (7). This impaired weight shifting towards the inner leg might hinder unloading of the outer leg, thereby disrupting the normal stepping sequence and triggering FOG (7).

During regular straight walking, external cues can alleviate FOG and restore spatiotemporal gait deficits (15). One plausible working mechanism is that cues shift motor control from a habitual to a goal-directed mode of control, redirecting neural processing to less-affected neural circuits (16). The cueing strategies currently used specifically for turning (8, 17-21) apply a different strategy, i.e. they all provide an external timing to which steps can be synchronized to, but lack cues designed to enforce goal-directed movements. Providing a visual goal to turn towards, possibly increases head-pelvis dissociation, restores COM shifting, and reduces FOG. Augmented reality (AR) displayed through smart glasses is particularly suited to provide interactive visual cues invoking goal-directed turning. Whether such cues are

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effective in reducing FOG during turning, and whether this is mediated by an effect on head-pelvis separation and medial COM shifting, is unknown.

This study aimed to assess whether AR visual cues could improve FOG and performance during turning in place in PD patients with FOG. Our primary objective was to assess whether AR visual cues influenced FOG severity compared to control conditions (no cues; and a conventional metronome). Our secondary objectives were to assess the influence of AR visual cues on axial kinematics, and on the scaling and timing of turning. We hypothesized that AR visual cues would reduce the percent time frozen and the number and duration of FOG episodes compared to the control condition without cues, with no differences compared to the conventional auditory cues. AR visual cues were expected to improve axial kinematics by increasing medial COM deviation, and advancing and increasing head-pelvis separation, compared to both control conditions. Step scaling (measured as step height and its variability) was thought to improve with AR visual cues compared to both control conditions. Turn timing (measured in cadence, peak angular velocity, stride time and its variability, and turn time) was expected to improve compared to the uncued control condition, with no effects compared to the auditory cues.

Methods

This study was performed in accordance with the guidelines of the Declaration of Helsinki (1964), was approved by the medical ethics committee Twente (NL66241.044.18), and registered in the Dutch trial registry (NTR7254; 2018-05-28).

Participant selection

Sixteen PD patients with a diagnosis of PD according to the UK Brain bank criteria (26), and a subjective experience of FOG on average more than twice a day were included (Table 1). Exclusion criteria were: significant cognitive impairment (mini mental state examination score [MMSE] <24 or frontal assessment battery [FAB] score <13); comorbidity causing severe gait impairments; severe bilateral visual or auditory impairments precluding the participant from using the cues; and an inability to perform a 180 degree turn

unaided. The following questionnaires were taken prior to testing: New Freezing of Gait Questionnaire (NFOG-Q) (27), the MDS-UPDRS part III (28), MMSE (29) and FAB (30). All participants provided written informed consent prior to their inclusion in the study.

Table 1 Clinimetrics

	median	IQR
Number of participants	16	
Age (years)	69	13
Gender (% male)	81	
Disease duration (years)	10	9
Years since FOG	4	9
LEDD (mg/day)	1220	776
UPDRS-part III	38	17
Hoehn and Yahr (II / III)	2	1
MMSE	29	2
NFOGQ	18	7
FAB	17	2

The median and interquartile ranges (IQR) quartiles are given, unless stated otherwise. FOG, freezing of gait; LEDD, levodopa equivalent daily dose; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III; MMSE, mini-mental state examination (range 0–30); NFOGQ, New Freezing of Gait Questionnaire (range 0–28); FAB, Frontal Assessment Battery (range 0–18). All questionnaires were rated while participants were at the end of a dopaminergic medication cycle ('end-of-dose').

Experimental set-up

A head-mounted AR device, the HoloLens (2017, developer version, Microsoft) (Figure 1B), was used for the holographic display of AR visual cues. The application generating the AR visual cues was custom-built with the game engine Unity (version 2017.1.0f3, Unity Technologies), a software development kit (version 10.0.14393.0, Windows), and Visual Studio (version 14.0.25431.01, Microsoft). Motion data were collected with the MVN Awinda motion capture system (Xsens, Enschede, the Netherlands) (22-24), consisting of 17 inertial measurement units (IMUs) with 3D gyroscopes, accelerometers, and

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magnetometers (60 Hz sampling frequency, 30 ms latency) attached to the feet (2), lower legs (2), upper legs (2), pelvis (1), hands (2), forearms (2), upper arms (2), sternum (1), shoulders (2), and head (1) with Velcro straps. These motion data were transmitted wirelessly to an experiment laptop with MVN studio 4.4 software installed, and saved for the post hoc calculation of kinematic parameters. Two video cameras were directed at the participant from different angles, one directed at the feet and legs, one providing a full-body record. Speakers played the metronome beat, and a beep indicating the start of a trial, at a clearly audible volume. A script built with MATLAB (version 2018a, Mathworks, Inc., Natick, MA, USA) was used to simultaneously play a beep signalling the start of the trial, start the motion capture recording, end the recording after a half turn was fulfilled, and register the timestamps, turning directions and cueing conditions.

Experimental procedure

Participants were tested 'end-of-dose', at or shortly after, the time they would usually take their (after)noon levodopa and were asked to postpone this levodopa intake until after the experiment. The experimental condition with AR visual cues ('Visual') consisted of a large yellow sphere displayed with an angle of 6° at 175 cm distance in AR, opening and closing in the turning direction at 2 Hz. The sphere, located in front of the user, moved along with head rotation, thereby 'consuming' a series of small yellow spheres displayed with an angle of 2° at 175 cm distance in AR, which were equally spaced at a semicircle around the participant (Figure 1C; additional video 1). Participants were instructed to rotate their bodies in the turning direction in order to 'consume' the small spheres with the large sphere. In one control condition ('Uncued'), no cues were applied. In the second control condition ('Auditory'), auditory cues were provided by playing a metronome beat at a frequency preferred by the participant, determined prior to the measurements. The HoloLens was worn in all conditions, but switched off in the control conditions. The experiment was divided into a training session, and two experimental sessions subdivided into 3 blocks each. The conditions were counterbalanced across each session, with one condition per block. Each block contained 15 trials in which participants performed a 180 degree turn around

their axis within a 50x50cm square taped onto the floor (Figure 1A), as fast as was safely possible (Figure 1A). The turn direction alternated between clockwise and counter clockwise. After the experiment, participants were asked about their previous experiences with cues, AR and virtual reality (VR), and their experiences with the cues and smart glasses in a structured interview.
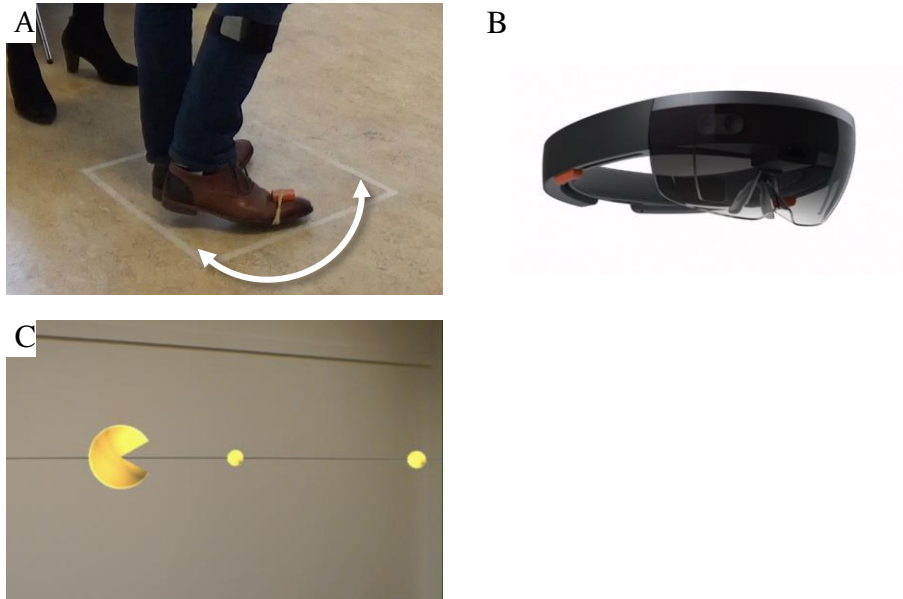

Figure 1 Experimental set-up. Participants performed 180 degree turns around their axes within a 50x50cm square (A), while wearing a HoloLens, a holographic augmented reality headset (B). Trials were performed under the conditions 'Visual', with augmented reality visual cues displayed through the HoloLens (C), 'Auditory', with a metronome beat played at a preferred fixed frequency (not illustrated), and without cues (not illustrated).

Study parameters

Parameters for FOG severity were: percent time frozen (PTF) and mean number and duration of FOG episodes (25). Axial kinematics were assessed with the maximum medial COM deviation, maximum head-pelvis separation, and time to maximum head-pelvis separation. Spatial and temporal turn

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parameters were: cadence, peak angular velocity, stride time, stride time coefficient of variation (COV), step height, step height COV, and turn time.

Signal preprocessing

Data processing was performed with MATLAB (version R2018a, Mathworks, Inc., Natick, MA, USA). Axial kinematic parameters (medial COM deviation and head-pelvis separation) were calculated from the signals of the head and pelvis IMU, and an automated estimation of COM-position outputted by MVN studio 4.4. Signal drift over the course of a recording session was corrected by removal of the linear trend in the orientation signal measured at the start of a trial, and by subtraction of the position at the start of a trial from the estimated COM-position and the pelvis position signals. Medial COM deviation was calculated as the maximum difference between COM position and centre-of-pelvis position projected to the inner side of the turn. Maximum head-pelvis separation was defined as the maximum angular difference in orientation of the head and pelvis sensors within the horizontal plane. Footstep-derived parameters (i.e. step height, stride time, and cadence) were calculated from the acceleration and the gyroscope signals of the foot sensors. Foot-ground contacts were detected with a general likelihood ratio test framework (26). FOG episodes were excluded from the calculation of footstep-derived parameters. Step height was calculated as the distance in meters between the ground and the highest vertical foot position during a foot swing. Stride time was defined as the time between two subsequent heel contacts with the same foot. Cadence was defined as the average number of steps per minute.

The number and duration of FOG episodes were scored by two independent raters blinded for the experimental condition from video recordings with the sound switched off. Disagreements were discussed until consensus was reached.

Statistical analysis

Statistical analyses were performed with MATLAB R2017b (Mathworks, Inc., Natick, MA, USA; statistics toolbox installed). Alpha was set at 0.05 and adjusted with the Bonferroni-Holmes method for pre-defined post hoc planned comparisons ('Visual' versus 'Control', and 'Visual' versus 'Auditory').

Extreme outlier values (defined as the values outside 3*interquartile range (IQR) below the first or above the third quartile) in kinematic parameters (except for the time to maximum head-pelvis separation) were attributed to technical causes and removed from the analyses. The stride time COV and step height COV were analysed only in trials with at least 3 strides. For all parameters, normality of distributions within and across participants were assessed by visual inspection of histograms and Q-Q plots, and tested by Shapiro-Wilk tests. Central tendency within participants was represented by the mean for FOG parameters, and the median for kinematic parameters. FOG parameters, maximum medial COM deviation, maximum head-pelvis separation, time to maximum head-pelvis separation, and turn time were non-normally distributed across participants and therefore analysed with the non-parametric Friedman test and post hoc Wilcoxon-signed rank tests for the effects of cues. The remaining parameters were analysed with the one-way repeated measures ANOVA and post-hoc paired T-tests. If Mauchly's test indicated that the assumption of sphericity was violated, p-values were corrected with epsilon calculated according to Greenhouse & Geisser. For stride time COV, step height, and step height COV, the analyses were repeated with exclusion of outliers (i.e. values outside 1.5*IQR below the first or above the third quartile), because these affected the normality of distributions. We report the p-value of the omnibus test (i.e. one-way repeated measures ANOVA or Friedman test) if there was a statistically non-significant group effect. Otherwise, the p-values of post hoc pairwise comparisons are reported. Participants who fulfilled the experiment were compared to those finishing a partial experiment with a Fisher's exact test for Hoehn-Yahr stage, Mann-Whitney U tests for other clinimetrics, FOG parameters and non-parametric kinematic parameters, and two-way mixed ANOVAs and a one-way ANOVA for parametric parameters. Consensus on the number and duration of FOG episodes between the two raters was assessed by a Spearman's rank order correlation.

Results

Twelve participants completed all 6 blocks, the four remaining participants finished after 3 to 5 blocks because of tiredness or time constraints. Compared

to those who completed the entire protocol, participants who performed only a partial experiment had experienced FOG for more years (median 13 vs. 2.5 years), and showed a higher medial COM deviation (mean 0.056 vs. 0.018 meter) for all cueing conditions.

One participant was excluded from the analyses of axial kinematics and turn scaling and timing parameters because of technical disturbances of the motion data.

FOG parameters

There was a high degree of consensus between raters on the rating of number $(rs(14) = 0.978, p < 0.0005)$ and total duration of FOG episodes $(rs(14) = 0.990, p < 0.0005)$ per participant. Fifteen participants experienced FOG at least once throughout the experiment. In those participants who experienced FOG, the mean percent time frozen ranged from 0.4 - 84.2%, with a group mean of 22.3% (all cueing conditions considered together).

AR visual cues did not significantly alter the percent time frozen (p 0.73), nor the mean number (p 0.73) and duration (p 0.78) of FOG episodes compared to the control condition without cues (Figure 2). All FOG parameters were higher with AR visual cues than with auditory cues (percent time frozen (p 0.01), mean number (p 0.02) and duration (p 0.007) of FOG episodes) (Figure 2).
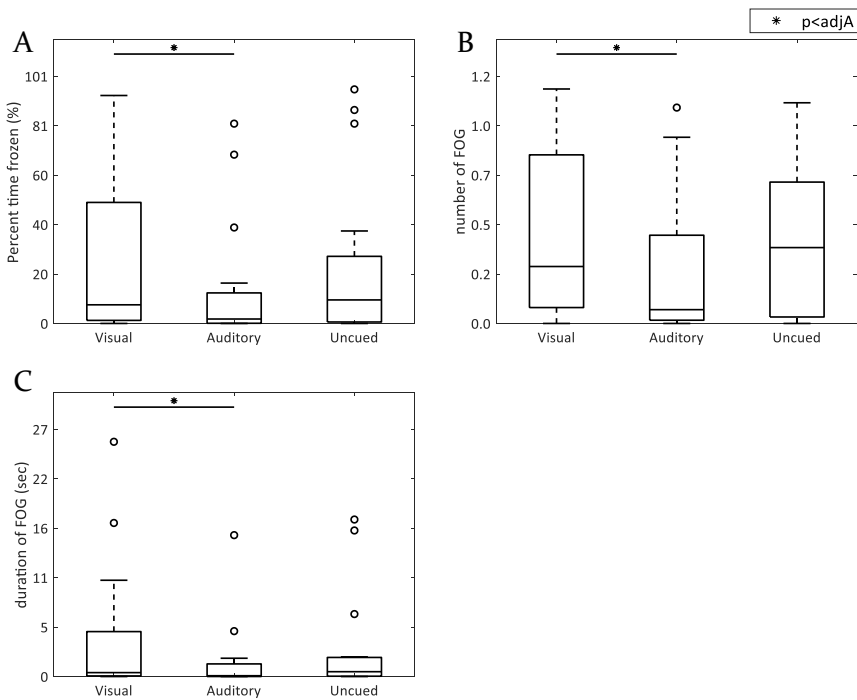
Figure 2. AR visual cues versus control conditions in FOG parameters. Boxplots showing the percent time spent frozen (A), and the mean number (B) and duration (C) of FOG episodes in the conditions with AR visual cues ('Visual'), a metronome ('Auditory') and no cues ('Uncued'). Significant pairwise comparisons are indicated by horizontal bars with asterisks.

Axial kinematics

The AR visual cues significantly increased the time to maximum head-pelvis separation (visual vs. uncued p 0.02; visual vs. auditory p 0.005) (Figure 4B), without effect on the maximum head-pelvis separation (p 0.08) (Figure 4A) and maximum medial COM deviation (p 0.09) (Figure 4C), compared to both control conditions.

Turn scaling and timing

AR visual cues significantly decreased peak angular velocity (visual vs. uncued *p* 0.03; visual vs. auditory *p* 0.02) (Figure 3B) and step height (visual vs. uncued *p* 0.02; visual vs. auditory *p* 0.007) (Figure 3E), and increased step height COV

(visual vs. uncued *p* 0.04; visual vs. auditory *p* 0.01) (Figure 3F), compared to the auditory and uncued conditions. Cadence (*p* 0.53) (Figure 3A), stride time (*p* 0.91) (Figure 3C), stride time COV (*p* 0.85) (Figure 3D), and turn time (*p* 0.08) (Figure 4D) were not significantly different between the AR visual cues condition and the control conditions.

Exclusion of outliers did not alter stride time COV, step height, and step height COV.
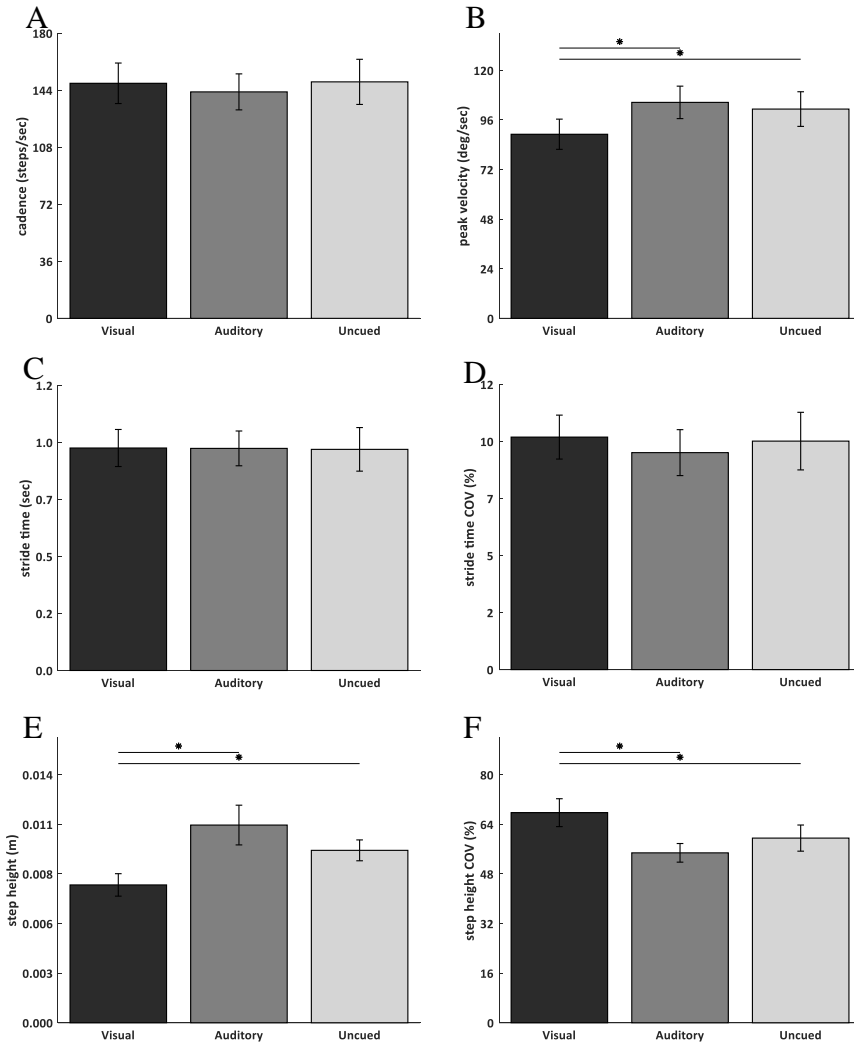
Figure 3. AR visual cues versus control conditions in normally-distributed kinematic parameters. Barplots showing the cadence (A), angular peak velocity (B), stride time (C), stride time coefficient of variation (D), step height (E), and step height coefficient of variation (F) in the conditions with AR visual cues ('Visual'), a metronome ('Auditory') and no cues ('Uncued'). Significant pairwise comparisons are indicated by horizontal bars with asterisks.

Figure 4. AR visual cues versus control conditions in non-normally-distributed kinematic parameters. Boxplots showing the maximum head-pelvis separation (A), time to maximum head-pelvis separation (B), maximum medial COM deviation (C), and turn time (D) in the conditions with AR visual cues ('Visual'), a metronome ('Auditory') and no cues ('Uncued'). Significant pairwise comparisons are indicated by horizontal bars with asterisks.
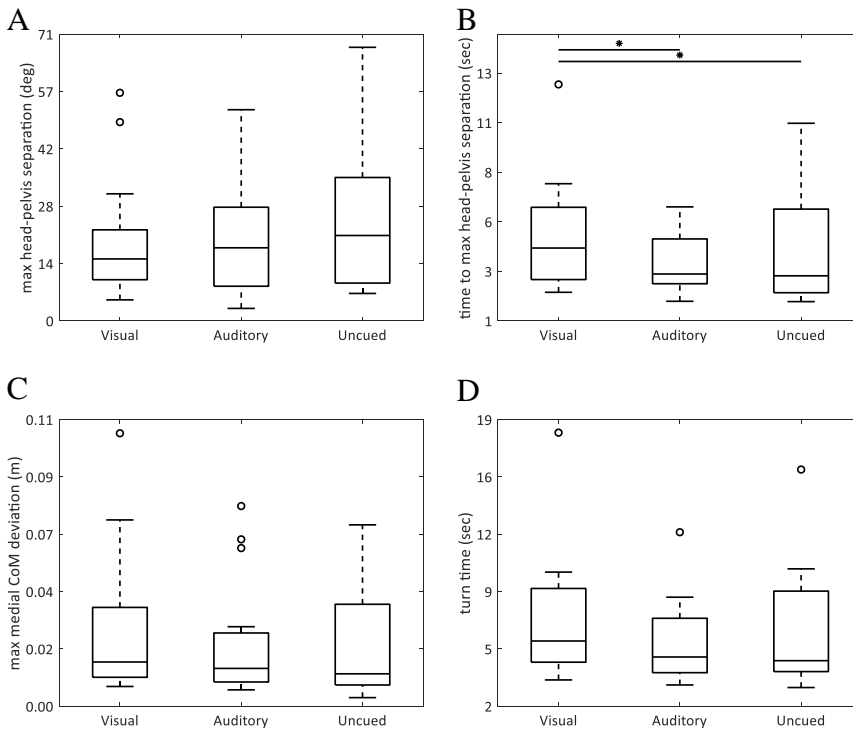
User experience with cues and smart glasses

Most participants (63%) were not accustomed to using cues in the home situation (additional Figure 1A). Six participants used visual cues, five participants auditory cues, at home (additional Figure 1A). Most participants had never seen an AR (73%) or virtual reality (VR) (67%) environment before (additional Figure 1B). When asked about their experience with the AR visual cues, 80% of participants agreed or strongly agreed that the AR visual cues were an easy goal to turn towards, 67% of participants reported that the cues

helped directing their attention towards turning, but only a minority (27%) felt that the cues helped them shifting their weights (additional Figure 1C). All participants strongly agreed that the color and shape of the visual cues were easy to differentiate, and 87% of participants had no problems localizing the AR visual cues. One participant (7%) indicated that the AR visual cues hindered normal sight, while 40% of participants reported that looking through smart glasses felt different from their normal sight (additional Figure 1C). A minority of participants felt that wearing smart glasses (regardless of cues) was distracting (13%) or restricting (13%), and all but one participant indicated to have easily gotten used to using smart glasses (additional Figure 1C).

Discussion

We aimed to assess whether AR visual cues improved FOG and turning in place performance in PD patients with FOG. FOG severity, axial kinematics, and turn scaling and timing were compared between an experimental condition with AR visual cues, and two control conditions (metronome and no cues). Contrary to our hypotheses, AR visual cues did not reduce FOG. In fact, FOG was worse with AR visual cues than with the auditory cues, which seemed due to a beneficial effect of the metronome rather than a detrimental effect of AR visual cues on FOG. Also in contradiction with our hypotheses, the AR visual cues worsened some measures of axial kinematics, and turn scaling and timing. We discuss several possible explanations for these findings.

First, stimulating goal-directed movement might by itself be insufficient to improve FOG and turning. Other characteristics of cues, such as their ability to aid in scaling or timing of movement (27), are possibly further prerequisites for cues to be effective. The timing aspect is often provided by auditory cues (8, 17-21), but could also be delivered by visual cues – e.g. by opening and closing the AR visual cues at the preferred stepping speed. To aid in scaling, both the current and targeted foot positions could be represented in AR, thereby providing information on the direction and size of the foot displacement required to reach the target.

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Second, the goal provided by the visual cues might have been too distinct from the actual goal of turning. In fact, AR visual cues might have introduced a dual task rather than an integrated turning strategy. The large sphere representing the body position implicitly stimulated body rotation. A more explicit goal, such as discrete targets to step towards, could be more effective. Indeed, a previous study applying transverse strips at a short-circle walkway demonstrated an improvement in FOG, step length, and cadence (28), although these cues not only stimulated goal-directed movement but aided in scaling as well.

Third, wearing smart glasses might have affected turn kinematics. Although wearing comfort of the HoloLens was considerably better than that of previous smart glasses (29), the glasses were still rather heavy. Participants might have kept their heads overly rigid to prevent the glasses from sagging or shifting. This might explain why no effect of cues on head-pelvis separation was found, contrasting earlier work showing a reduction in head-pelvis separation induced by auditory cues (21). Likewise, such increased axial rigidity might have prevented the cues from increasing medial COM shifting. Confirming that smart glasses indeed altered turn kinematics would require a comparison between turning with and without smart glasses.

Fourth, the participants might have been insufficiently familiarized with the smart glasses and cues. Participants were allowed to practice until they felt comfortable with the task and conditions, and all but one participant indicated they easily got used to using the smart glasses. Nevertheless, they might not have mastered using the cues adequately. Indeed, for two-thirds of participants this was their first encounter with virtual or augmented reality, and only a third of participants used cues at home.

A limitation to this study is that participants were not selected for a known cueing responsivity. That two-thirds of our participants were not accustomed to using cues might have been due to unfamiliarity with cues, but also to a previously experienced resistance to cueing effects. Selecting only those patients with a recognized response to cues would increase the potency of

experimental cues, but reduce generalizability of the results to patients with an unknown response to cues.

Another limitation to this study is the absence of control groups. The inclusion of healthy individuals or PD patients without FOG would have allowed to infer whether effects of the cues on axial kinematics and turn timing and scaling were specific to PD or FOG.

Conclusion

The Augmented Reality visual cues in this study did not improve FOG, and impaired axial kinematics, and turn scaling and timing. Most likely, it takes more than stimulating goal-directed movement to alleviate FOG and improve turning. Whether visual cues delivered through augmented reality earn a place in the repertoire of cueing strategies remains to be established.

Abbreviations

FAB, Frontal Assessment Battery; FOG, freezing of gait; MMSE, mini-mental state examination; N-FOGQ, New Freezing of Gait Questionnaire; PD, Parkinson's disease; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III (motor examination); AR, augmented reality; VR, virtual reality.

Supplementary material

Supplementary video material is accessible through http://hdl.handle.net/11633/aacy3qb4.

Supplementary video 1 AR visual cues during turning
Demonstration of the AR visual cues during a turn right followed by a turn left. Here, a hand gesture starts the AR visual cues. During the experiments the cues were started with a remote controller by the researcher, not requiring any action from the participant. Small spheres are equally spaced at a half circle around the participant. Head rotation causes a large sphere to move forwards on a semicircular path, 'consuming' the small spheres on its way.

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A

Cues used per participant
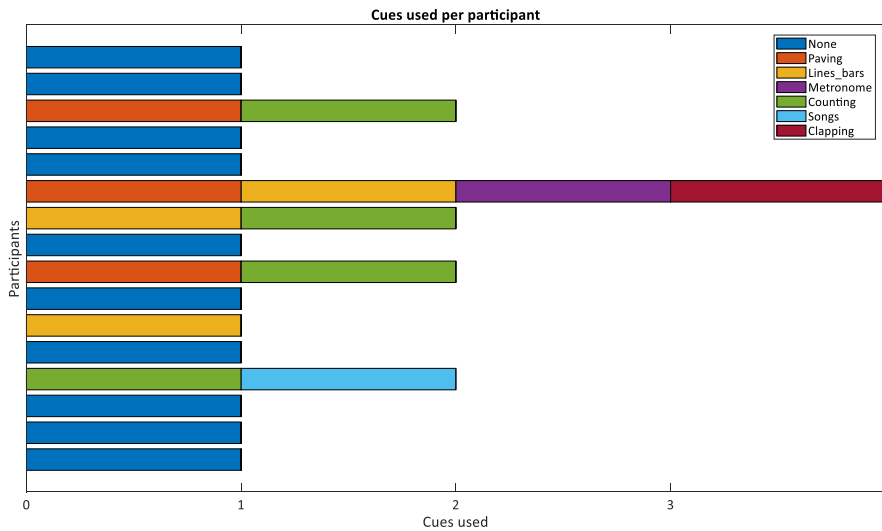
B

How often have you seen an AR environment before?

1-2 x:27%

0 x:73%
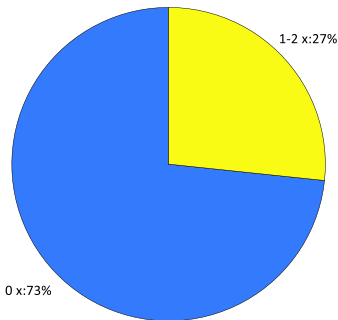
How often have you seen a VR environment before?

1-2 x:33%

0 x:67%
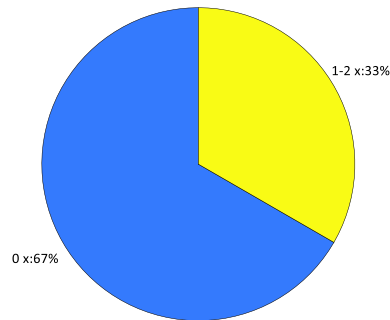
Additional figure 1A and B. Answers structured interview.
(A) Stacked bar plot representing the use of cues by participants in the home-situation. Each horizontal bar represents one participant. The use of multiple cues by one participants is illustrated as multicolored stacked bars. (B) Pie charts illustrating how often participants had previously seen an augmented reality (AR, left) or virtual reality (VR, right) environment before.
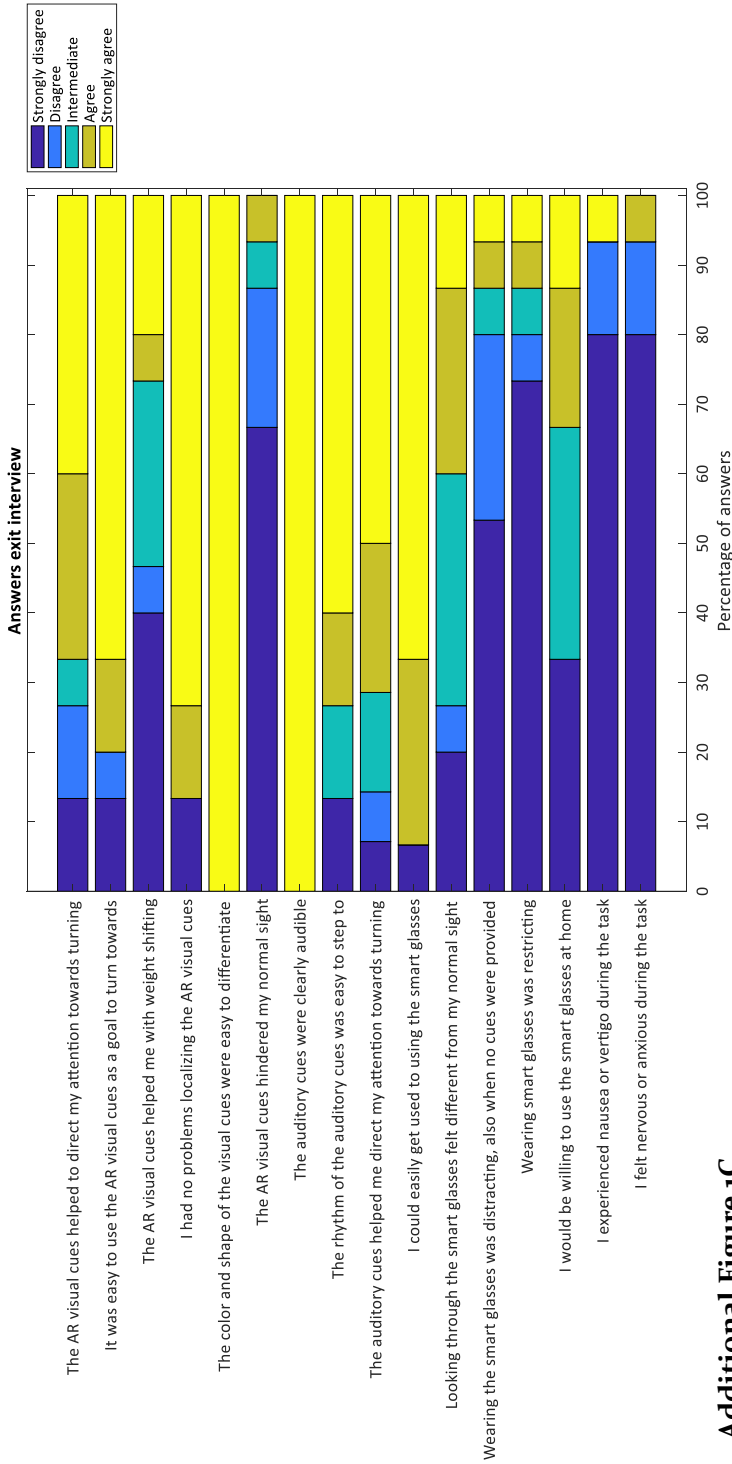
Additional Figure 1C

Stacked bar plot representing the percentage of answers on a 5-point Likert scale, from 'Strongly disagree' to 'Strongly agree', to questions about the experimental cues and smart glasses. All participants fulfilled part A and B of the structured interview, 15 out of 16 participants fulfilled part C.

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PART III

RESEARCH PARADIGMS

TO STUDY CUEING

CHAPTER 9

VALIDATION OF THE AUDITORY STROOP TASK

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Abstract

Background: The development of treatments for freezing of gait (FOG) in Parkinson's disease (PD) requires experimental study set-ups in which FOG is likely to occur, and is amenable to therapeutic interventions. We explore whether the 'Auditory Stroop Task' (AST) can be used to increase cognitive load (and thereby elicit FOG), simultaneously with visual cues (as a therapeutic intervention for FOG). We additionally examined how these two contrasting effects might interact in affecting gait and FOG parameters.

Objectives: We investigated whether: (1) the 'Auditory Stroop Task' (AST) influences gait in healthy elderly and persons with PD who experience FOG, and increases the frequency of FOG events among PD patients; (2) the AST and visual cues interact; and (3) different versions of the AST exert different cognitive loads.

Methods: In 'Experiment 1', 19 healthy elderly subjects performed a walking task while performing a high and low load version of the AST. Walking with a random numbers task, and walking without cognitive load served as control conditions. In 'Experiment 2', 20 PD patients with FOG and 18 healthy controls performed a walking task with the AST, and no additional cognitive load as control condition. Both experiments were performed with and without visual cues. Velocity, cadence, stride length, and stride time were measured in all subjects. FOG severity was measured in patients.

Results: Compared to the control conditions, the AST negatively affected all gait parameters in both patients and controls. The AST did not increase the occurrence of FOG in patients. Visual cues reduced the decline in stride length induced by cognitive load in both groups. Both versions of the AST exerted similar effects on gait parameters in controls.

Conclusions: The AST is well-suited to simulate the effects of cognitive load on gait parameters, but not FOG severity, in gait experiments in persons with PD and FOG.

Introduction

Cognitive dual tasks negatively affect gait in elderly people (1-3). The relationship between dual tasks and gait is influenced by factors such as age, attentional resources, neurological comorbidity, and the type and complexity of the dual task applied (1, 2, 4). Compared to age-matched healthy controls, persons with Parkinson's disease (PD) are more susceptible to gait interference by dual tasks (5, 6). This effect is even more pronounced in the presence of freezing of gait (FOG) (7, 8), a debilitating motor symptom occurring predominantly in advanced stages of PD (5, 9). External cues such as transverse bars on the floor can oppose the effects of dual tasks on gait parameters in persons with PD (10).

In experimental settings, cognitive dual tasks can be applied to simulate the domestic situation where dual tasks (e.g. talking while walking) can worsen gait, or to provoke FOG in persons with PD. Meanwhile, external cues are being investigated for their beneficial effects on gait and FOG, and their usability in daily life(11-13). In PD, dual tasks and external cues are often studied simultaneously (3, 10, 14-19). In such studies, the cognitive task applied would ideally meet the following criteria. First, the task calls upon executive function, as this is an important determinant of FOG severity (20) and gait performance under dual task conditions (21). Second, the task should not introduce a rhythm, to prevent interference with the external cues under investigation. Third, the paradigm does not interfere with vision in studies involving visual cues. Fourth, considering the age range in which PD occurs, the task should be insusceptible to age-related sensorineural hearing loss (22). Fifth, the level of difficulty of the task should be independent of the level of education. Sixth, the task should provide the possibility to incorporate additional instructions (such as 'start walking') without having to add another task. Lastly, any interactions between the external cues and gait parameters are known. Current paradigms used to increase cognitive load (4) do not meet all of these criteria. For example, the random numbers task (RNT) applied previously (10) does not allow for additional commands to be enclosed within the task. The classic auditory Stroop task (23) involving high and low pitched sounds depends on hearing sensitivity (22). A variant of the auditory Stroop

task (AST), in which the words 'man' or 'woman' are spoken by a male or female speaker (24), is likely to be less susceptible to hearing quality and potentially fits the criteria described above.

The AST requires validation for it to be used in gait experiments in healthy elderly and PD patients.

The primary aim of this study was to assess whether the AST was effective in influencing gait parameters in healthy elderly and PD patients, and whether it would enhance the likelihood of FOG occurrence in persons with PD. The secondary aim was to assess whether visual cues interfered with the influence of the AST on gait parameters in both PD patients and controls. The tertiary aim was to assess whether the size of the cognitive load exerted by the AST could be manipulated by different versions of the task. These aims were investigated in two gait experiments. To minimize the number of conditions and trials, the AST was first validated against an established cognitive load task (random numbers task, RNT) and no additional cognitive load in healthy elderly (experiment 1). Then, the AST was compared to a control condition without cognitive load in PD patients and in controls (experiment 2). Both experiments measured the influence of the different cognitive loads on gait parameters in both the presence and absence of visual cues. Experiment 2 additionally measured FOG in PD patients.

We hypothesized that: 1) the AST would be at least as effective as the RNT in influencing gait parameters in controls; 2) the AST would influence gait in both patients and controls, and in patients the most; 3) the AST would increase FOG occurrence in patients; 4) visual cues would reduce the influence of the AST on gait both in patients and controls; and 5) a high load version of the AST would exert a larger effect on gait parameters in controls than its low load counterpart.

Materials and methods

This study was performed in accordance with the guidelines of the Declaration of Helsinki (1964). All subjects provided written informed consent prior to inclusion. Both experiments were approved by the local ethics committee of the University of Twente. Experiment 2 was approved by the medical ethics

committee Twente (NL60687.044.17) and registered in the Dutch trial registry (NTR6409).

Experiment 1

Study population

20 healthy subjects ('controls') were included (Table 1). Inclusion criteria were: age 50 years and older, capable of walking unaided, no comorbidities affecting gait impairment, and intact vision and hearing.

Table 1 Clinical characteristics of the participants

	Experiment 1	Experiment 2	
	Healthy controls Median (Q1 – Q3)	Healthy controls Median (Q1 – Q3)	PD patients Median (Q1 – Q3)
Number of participants	19*	18	20
Age (years)	65 (59.8 – 68.8) [a]	67.5 (62 - 70) [a,b]	70.5 (63.5 - 73) [b]
Gender (% male)	63.2 [c]	50 [c,d]	85 [d]
Disease duration (years)			11 (7.5 - 16)
Years since FOG (years)			4 (2.5 – 6.5)
LED (mg/day)			1128 (901.5 - 1359)
UPDRS-part III			39.5 (31.5 – 47.5)
UPDRS-PIGD			4.5 (3 - 7)
Hoehn and Yahr (II / III)			12 / 8
MMSE			29 (27 - 30)
N-FOGQ			21 (16 - 25)
FAB			16 (15 - 17)

The median and first (Q1) and third (Q3) quartiles (i.e. the boundaries of the interquartile range) are given, unless stated otherwise. Comparisons for age: [a] controls in experiment 1 vs. experiment 2, $p>0.05$; [b] controls vs. patients in

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experiment 2, p>0.05. Comparisons for gender: [c] controls in experiment 1 vs. experiment 2, p>0.05; [d] controls vs. patients in experiment 2, p=0.035.

*Data of one participant in experiment 1 were discarded from analysis because of technical issues.

PD, Parkinson's disease; FOG, Freezing of Gait; LED, levodopa equivalent dose; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III; UPDRS-PIGD, Unified Parkinson's Disease Rating Scale - Postural instability and gait disorder; MMSE, mini-mental state examination (range 0 - 30); N-FOGQ, New Freezing of Gait Questionnaire (range 0-28); FAB, Frontal Assessment Battery (range 0-18). All questionnaires were rated while participants were OFF medication.

Experimental procedure

The walking task consisted of a 15 m walk through a corridor, a 180° turn, and walking back at a comfortable pace. Trials lasted 30 seconds and their start and end were signalled by recorded voice commands. Participants were informed that the distance traveled and whether or not they reached a turn were not of importance. The walking tasks were performed under five different cognitive load conditions (Figure 1): high and low cognitive load AST ('AST_high' and 'AST_low') and RNT ('RNT_high' and 'RNT_low'), and no additional cognitive load ('noCL'). In the AST_high, recorded male and female voices speaking the Dutch translations of the words 'man' and 'woman' were played through speakers. Congruent Stroop-cues, i.e. 'man' by a male voice, represented the cue to start or continue walking. Incongruent Stroop-cues, such as 'woman' spoken by a male voice, indicated to (continue to) stand still. Per trial were 3 or 4 Stroop-cues, of which at least 2 were incongruent, played with random timing and order. The AST_low was similar to the AST_high, apart from that it contained only the male and not the female voice. In the RNT, records of spoken numbers 1 up to 9 were played through speakers in a random order and at random time intervals. Participants were instructed to mentally count how often two (RNT_high) or one (RNT_low) given number(s) occurred in the sequence. This count was asked after the trial to verify adherence to the task, but no feedback on the performance was given. In the

noCL, no cognitive load was added. Trials were performed in the presence ('VC') or absence ('noVC') of visual cues, consisting of white bars of 18mm x 18mm x 914mm, equally spaced on the floor at 40% of the participant's height, rounded to the nearest 5cm (25). An experiment was divided into two blocks ('noVC' and 'VC'). Each cognitive load condition ('AST_high', 'AST_low', 'RNT_high', 'RNT_low', and 'CC') occurred twice per block. The order of the visual and cognitive conditions was counterbalanced across subjects.
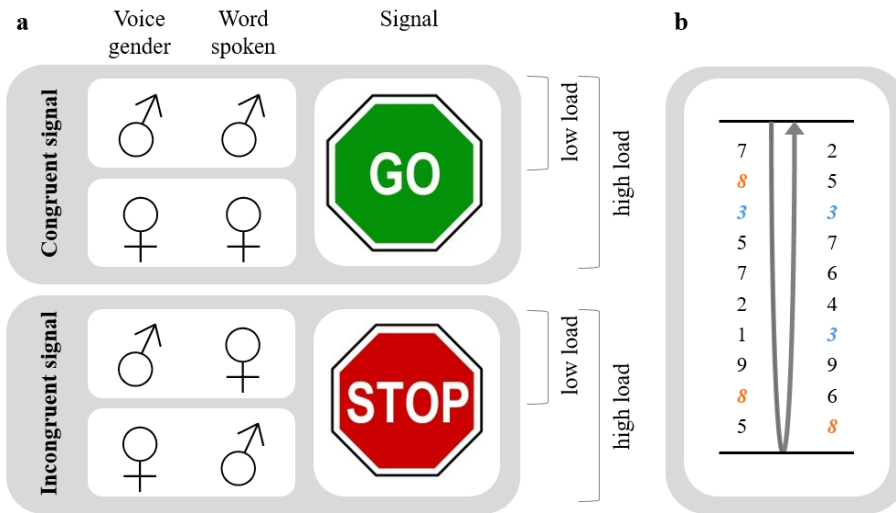

Figure 1. Cognitive load conditions. a. Auditory Stroop Task (AST) with the congruent signals (e.g. male voice speaking the Dutch translation of 'man') signaling the participant to start or continue walking, and incongruent signals (e.g. 'woman' spoken by a male voice) signaling to stand still. The high load AST ('AST_high') consisted of only the male voice, the low load AST ('AST_low') of both a male and female voice. b. Random Numbers Task (RNT) in which the numbers 1 to 9 were played in a random order and at random time intervals. Participants were instructed to mentally count how often two ('RNT_high') or one ('RNT_low') given number(s) occurred in the sequence (here '3' and '8', represented in orange and blue).

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Experiment 2

Study population

We included 20 patients fulfilling the UK Brain Bank criteria for PD, and experiencing FOG minimally twice a day (defined as a score of 3 on question 2 of the New Freezing of Gait Questionnaire [NFOGQ] (26)). (Table 1). Exclusion criteria included a mini mental state examination (MMSE) score <24, executive dysfunction defined as a frontal assessment battery (FAB) score <13, comorbidities causing severe gait impairment, or an inability to walk 150 meters unaided. Patients were tested during the dopaminergic OFF-state, at least 12 hours after the last intake of dopaminergic medication. In addition, 18 age-matched healthy controls without impairments of gait, vision or hearing, who had not participated in the first experiment, were included.

Experimental procedure

Walking tasks were similar to those described at 'Experiment 1', with the exceptions that the corridor was 30m long, and that chairs were placed back-to-back 50 cm apart at 10m and 20m to create passages. The walking tasks were performed under the cognitive load conditions 'AST_high' and 'noCL', and the visual cueing conditions 'VC' and 'noVC' as described above. Experiments were divided into two blocks ('VC' and 'noVC'), subdivided into two sessions ('AST_high' and 'noCL'), with 6 trials per session. The order of the blocks and sessions was counterbalanced.

Data acquisition and preprocessing

In both experiments, motion data were collected with the MVN Awinda motion capture system (Xsens, Enschede, the Netherlands)(27-30), consisting of 17 IMUs with 3D gyroscopes, accelerometers, and magnetometers (60 Hz sampling frequency, 30 ms latency) attached to the feet (2), lower legs (2), upper legs (2), pelvis (1), hands (2), forearms (2), upper arms (2), sternum (1), shoulders (2), and head (1). Data were transmitted wireless to a laptop with MVN studio 4.4 software installed. Raw accelerometer and gyroscope data, together with orientation and position data calculated by MVN studio, were exported to MATLAB R2017b (Mathworks, Inc., Natick, MA, USA; statistics

toolbox installed) for the offline calculation of gait parameters (31), and statistical analysis.

Raw data were organized within the Global reference frame (32). The gait events 'heel contact' and 'toe off' (33) were detected. Noise, extreme outlier values (outside median plus and minus 3*IQR) due to technical reasons, turning movements (34), gait arrests following incongruent Stroop-cues, step hesitations (defined as interruptions of alternate stepping), and FOG episodes (as assessed by clinical video annotation) were removed. Data of trials in which calibration of the MVN Awinda motion capture system was qualitatively poor were corrected by applying a correction factor for walked distance based on rightly calibrated trials of the same participant. The representation of the relative position of the feet was sensitive to the quality of calibration, affecting step but not stride parameters. Therefore, stride length and stride time, but not step parameters, were analysed.

In experiment 2, the number and duration of FOG were scored by two independent and experienced raters from video recordings with the sound switched off. Disagreements were discussed until consensus was reached.

Study parameters

Gait parameters calculated in both experiments were: stride length and time plus their coefficients of variation, gait velocity, and cadence. In the PD group, the number of FOG episodes (nrFOG) and the percent time frozen (PTF)(35) were measured. Gait parameters were contrasted for 1) the AST vs. the RNT (experiment 1), 2) the AST vs. the noCL in the conditions without and with visual cues (experiment 1 and 2), 3) the interaction of cognitive load and visual cues (experiment 1 and 2), and 4) the effects of high versus low cognitive load (experiment 1). For contrast 1 - 3 in the first experiment were high and low load versions of the AST and the RNT combined into 'AST' and 'RNT'. FOG parameters were contrasted for the AST vs. the noCL in the conditions with and without visual cues (experiment 2).

Statistical analysis

A statistical level of α=0.05 was applied. Groups were compared for age with a two-sample t-test, and for gender with a Fisher's exact test. The effects of

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cognitive load, visual cues, and high versus low cognitive load were evaluated by the Sign test. The interaction of cognitive load and visual cues was analysed with the two-way repeated measures ANOVA. The effects of participant class were assessed by the three-way mixed model ANOVA (within-subject factors: cognitive load condition [AST vs. noCL] and visual cueing condition [VC vs. noVC]; between-subjects factor: participant class [patient vs. control]). Outliers were defined as values outside the median plus and minus 1.5 times the interquartile range. In the presence of outliers, analyses were performed with and without the participants in whom outliers occurred. Data represented in tables and figures include participants with outlier values. Normality of data distribution was assessed with visual inspection of histograms, boxplots and Q-Q plots, and checked with the Shapiro-Wilk test. If data of a condition were missing due to technical issues, the mean value of the opposite VC condition (e.g. 'AST/VC' instead of 'AST/noVC') was taken and analyses were performed with and without the participant in which the missing condition occurred. Consensus on the number and duration of FOG episodes between the two raters was assessed by a Spearman's rank order correlation.

Results

In experiment 1, data of one participant were discarded from the analyses because of technical issues. In one participant in experiment 1, data were missing for one condition (RNT_low, no visual cues). Imputation of data from the opposite cueing condition (RNT_low, with visual cues), or exclusion of this participant from the analysis resulted in similar results. Analyses were pursued including this participant, with imputed data.

Effects of the AST on gait parameters and FOG

AST vs. RNT in healthy controls

The AST resulted in a stronger reduction of velocity and cadence, and a stronger increase of the coefficients of variation of stride length and stride time (Table 2, Figure 2) than the RNT. Subsets of participants experienced lower stride length and higher stride time in the AST compared to the RNT in the absence of visual cues. However, because the majority of participants had

similar stride lengths and stride times in both conditions, the differences between the medians of the conditions were equal or close to zero (Table 2).

Table 2. Results per aim/hypothesis

Contrast	Exp	Group	Cues	Velocity (m/s)	Cadence (st/min)	Stride length (m)	Stride time (s)	Stride length COV	Stride time COV
AST vs. RNT	1	HC	noVC	-0,07 **	-4,80 **	0,01 **	0,00 **	2,99 **	2,08 *
			VC	-0,01	-9,48 *	0,02	0,04 *	2,54 **	1,41 *
AST vs. noCL	1	HC	noVC	-0,15 **	-4,51 *	-0,07 **	0,01 **	2,86 **	1,72 **
			VC	-0,05 *	-13,59 **	0,02	0,09 **	2,15 *	1,56 **
	2	HC	noVC	-0,08 **	-7,01 **	-0,07 **	0,00 *	6,51 **	3,76 **
			VC	-0,14 **	-13,8 **	-0,02	0,08 **	4,18 **	3,86 **
	2	PD	noVC	-0,19 **	-18,1 **	-0,07 **	0,08 **	13,60 **	6,12 **
			VC	-0,13 **	-17,2 **	-0,08 *	0,16 **	10,22 **	5,64 **
	2	PD vs HC (F-ratio)	noVC & VC	1,787	0,472	6,510 *	3,358	2,671	1,042
Interaction AST x cues (F-ratio)	1	HC		8,591 **	4,890 *	27,866 **	4,240	2,388	0,365
	2	HC		0,121	3,835	8,648 **	7,486 *	4,697 *	0,705
	2	PD		4,018	0,037	8,875 **	0,443	0,742	0,197
	2	PD vs. HC		3,182	1,583	1,818	0,590	0,226	0,007
High vs. low AST	1	HC	noVC	0,01	0,08	-0,01	0,00	3,16	0,16
			VC	-0,06	-4,90	-0,01	0,00	0,58	-0,40

Differences between the median values of conditions, unless stated otherwise. Asterisks indicate statistical significance; *p<0.05, **p<0.01. AST, Auditory Stroop Task (high and low load, unless stated otherwise); COV, coefficient of variation; Exp, experiment; high, high cognitive load; low, low cognitive load; noCL, no additional cognitive load (control); noVC, no visual cues; RNT, Random Numbers Task (high and low load, unless stated otherwise); VC, with visual cues
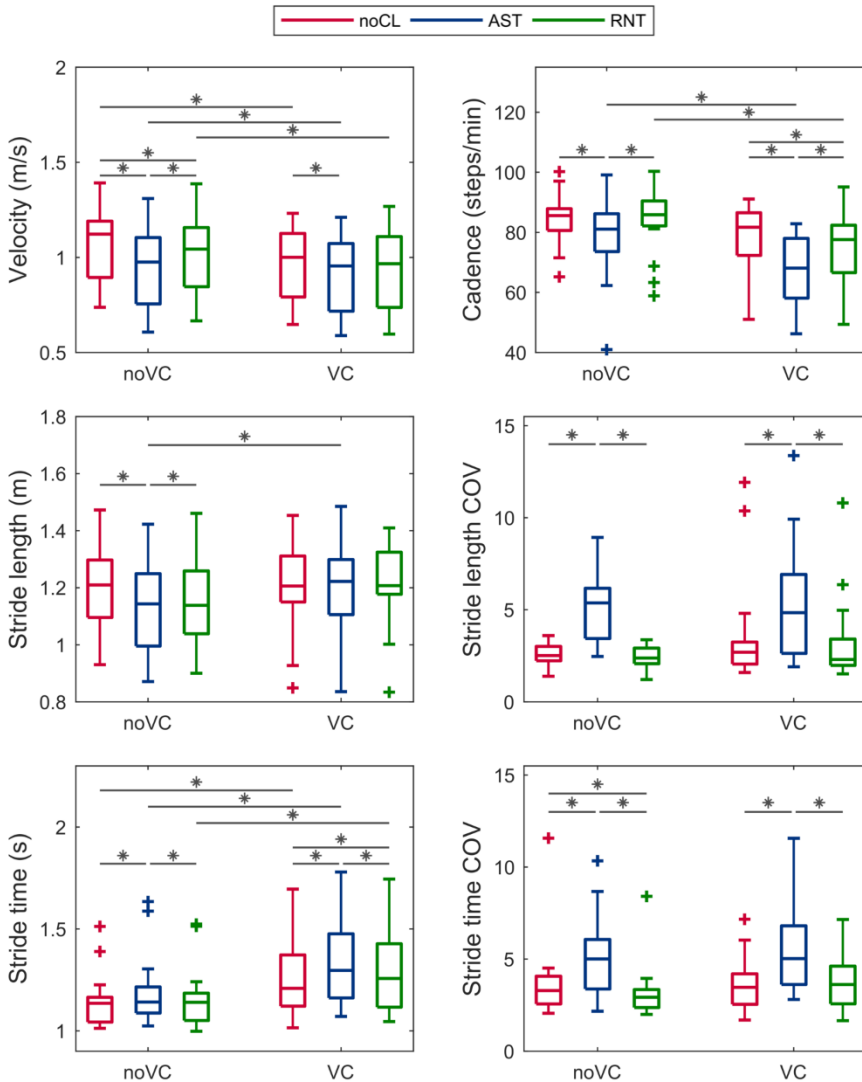
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Figure 2. Gait parameters under different conditions of Experiment 1. Boxplots of the gait velocity (m/s), cadence (steps/min), stride length (m), stride length coefficient of variation (COV), stride time (sec), and stride time coefficient of variation (COV). Cognitive load conditions are illustrated in red (control cognitive load, noCL), blue (Auditory Stroop Task, AST), and green (Random Numbers Task, RNT). Conditions with no visual cues ('noVC') are displayed at the left sides of the plots, conditions with visual cues ('VC') at the right sides. Asterisks above indicate significant differences between cognitive load conditions (within the left or right half of a plot), and between visual cueing conditions (crossing the midline of the plot).

Effects of the AST on gait parameters in PD patients and healthy controls

In the absence of visual cues and compared to the condition with no additional cognitive load, the AST reduced velocity, cadence and stride length, and increased the coefficients of variation of stride time and stride length in both PD patients and healthy controls (Table 2, Figure 2 and 3). The AST increased stride time in PD patients and in a subset of healthy controls, whilst the majority of healthy controls had similar stride times in both conditions (causing a difference between the medians close or equal to zero) (Table 2).
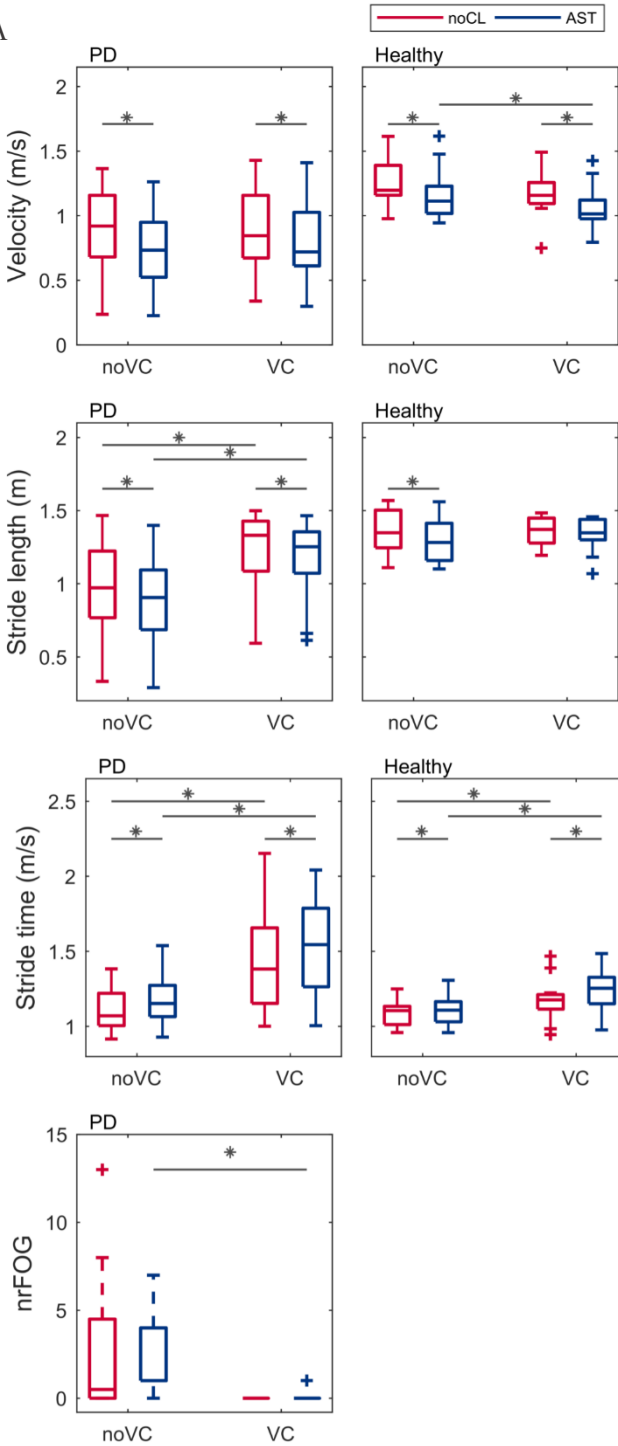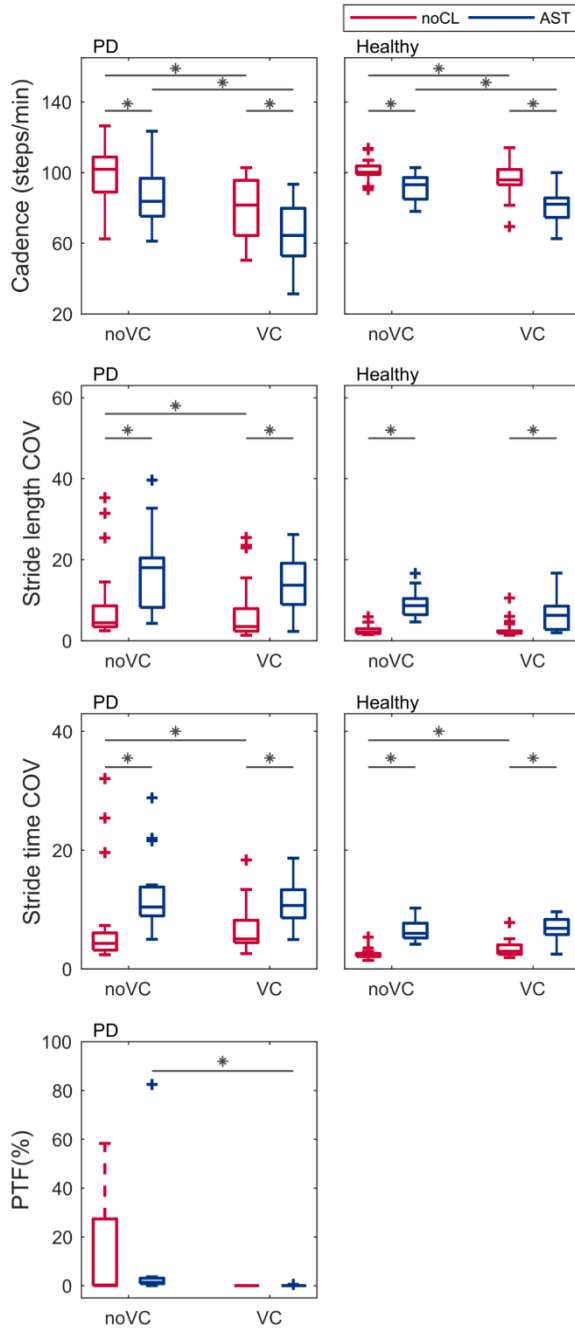
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Figure 3A

Figure 3B

Figure 3 (A & B). Gait parameters in different conditions of Experiment 2. Boxplots of the gait velocity (m/s), cadence (steps/min), stride length (m), stride length coefficient of variation (COV), stride time (sec), and stride time coefficient of variation (COV) for persons with Parkinson's disease and freezing of gait ('PD') and healthy control subjects ('Healthy'). The number of freezing of gait episodes (nrFOG) and percent time frozen (PTF) are given for PD patients. Cognitive load conditions are illustrated in red (control cognitive load, noCL), and blue (Auditory Stroop Task, AST). Conditions with no visual cues ('noVC') are displayed at the left sides of the plots, conditions with visual cues ('VC') at the right sides. Asterisks above indicate significant differences between cognitive load conditions (within the left or right half of a plot), and between visual cueing conditions (crossing the midline of the plot).

Effects of the AST on FOG occurrence in PD patients

The degree of consensus on rating the number [$rs(18)=0.657$, $p=0.001$] and duration of FOG [$rs(18)=0.668$, $p=0.001$] between raters was high. Eight PD patients experienced FOG at least once in the experiment, with in total 43 FOG episodes (median 1.5, first quartile 1, third quartile 8.5), which lasted 371.5 seconds (median 3.5 sec, first quartile 2.5 sec, third quartile 52.5 sec) in total. One participant accounted for 46.5% of all FOG episodes and was frozen for 35.2% of the time, and was considered an extreme outlier.

Compared to the condition with no additional cognitive load, the AST did not increase the number of FOG episodes (difference between medians 0.5, p-value 1.00) nor the percent time frozen (difference between medians 1.11, p-value 0.73) in the absence of visual cues, regardless of whether the extreme outlier was excluded. In the presence of visual cues, FOG occurred twice in one participant in the AST condition, and never in the cognitive control condition (difference between medians 0.0, p-value 1.00).

Interaction between the AST and visual cues

Outlier values occurred in a minority of trials across study parameters and participants. If results changed significantly upon exclusion of participants in whom outlier values occurred, this has been described accordingly.

Both visual cues and the AST reduced velocity in the controls in the first experiment, with an only modest additional decrease due to the AST in the presence of visual cues (Table 2, Figure 2, Supplementary Table 1). However, these findings were not reproduced in both controls and patients in the second experiment (Table 2, Figure 3, Supplementary Table 2). The reduction in cadence caused by the AST was enforced in the presence of visual cues in both patients and controls, although statistical significance was only reached in the controls in the first experiment. The AST reduced stride length in the absence of visual cues (Table 2, Figure 2 and 3, Supplementary Table 1 and 2). Visual cues centred stride length around twice the set distance between the cues. This was unchanged by the AST in controls, whilst in patients the AST caused a modest additional reduction in stride length in the presence of visual cues (Supplementary Table 1 and 2, Figure 2 and 3). However, if participants with outlier values for stride length (N = 1) were removed from the analyses, significance of the interaction effect was lost in controls in the second experiment. There was a trend towards an increase in stride time due to the AST in the presence of visual cues. However, this was only statistically significant for controls in the second experiment. In the first experiment, statistical significance was reached only if participants with outlier values for stride time (N = 2) were excluded from the analysis (p = 0.004 without outliers; p = 0.054 including outliers). Considering the influence of outliers, and the inconsistent results between the two experiments, we warrant caution in interpreting this result. Only significant in controls in the second experiment, visual cues reduced the increase of the coefficient of variation of stride length caused by the AST. However, when participants with outlier values were excluded (N = 6), statistical significance for the interaction effect was lost. No interaction effects between the AST and visual cues existed for the coefficient of variation of stride time in both patients and controls. No statistically

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significant effects of participant class (controls and patients) were found on the interaction between the AST and visual cues on any of the gait parameters.

Effects of high vs. low cognitive load AST
None of the gait parameters differed statistically significant between the high and low load AST in controls (Table 2, Figure 2, Supplementary Table 1).

Discussion

This study primarily investigated whether the AST could be used to alter gait parameters in healthy elderly and in PD patients who experience FOG, and FOG parameters in PD patients, by increasing cognitive load. The AST caused both controls and patients to walk slower, with shorter and more variable steps. These results are consistent with prior studies reporting lower gait speed, shorter stride length, lower cadence and increased stride time and stride time variability under dual task conditions in controls (4), and PD patients (5). The AST impacted gait parameters more than the RNT did, suggesting that the AST exerted the highest cognitive load. Alternatively, the additional motor task (i.e. gait cessation and initiation) present in the AST, but not the RNT, might compete for the same processing resources that gait control and the cognitive task call upon, leading to competition for limited resources and hence a deterioration in performance of (one of) the tasks, here walking (5). These findings support our hypothesis that the AST influences gait in healthy elderly and PD patients. However, the AST did not increase the likelihood of FOG occurrence.

The secondary aim was to assess whether visual cues interfered with the influence of the AST on gait parameters in controls and PD patients. An interaction effect between cognitive load and visual cues was strongest and most consistent for stride length in both patients and controls. Both visual cues and cognitive load influenced stride length, but when applied simultaneously there was no additional effect of the AST on stride length in controls, and a modest additional reduction of the AST in patients. In healthy controls, interaction effects were additionally found for velocity, cadence, stride time, and stride length coefficient of variation, but the results were inconsistent between the two experiments and require replication in larger

participant groups to assess their validity. A previous study found significant interactions between a dual task and visual cues for step length, step time, velocity and double support time percentage in persons with PD and FOG, indicating that visual cues prevented these gait parameters to be affected by dual tasks (10). Our hypothesis that visual cues reduce the influence of cognitive load on gait and FOG was true for stride length, but not for the other gait parameters and FOG.

Our tertiary aim was to assess whether the size of the cognitive load exerted by the AST could be manipulated by different versions of the task. The high versus low load AST impacted gait parameters similarly, indicating that similar cognitive loads had been exerted. Neither version of the AST increased FOG severity in patients. Further work remains needed to identify which type of secondary task is better able to increase FOG occurrence and severity in gait experiments.

The main limitation of this study was the low number of participants, reducing the statistical power. Furthermore, patients and controls were not matched for gender. Although a previous study involving a gender-based auditory Stroop task found no significant differences in performance between male and female participants (36), we cannot exclude gender to have influenced differences found between patients and controls. In addition, a more thorough examination of cognitive function in both patients and controls would have allowed for a more detailed characterization of the participants.

We recommend future studies involving the AST to include more participants, and to match not only for age but also for gender and cognitive functioning.

Conclusions

In conclusion, this study shows that the AST is well-suited to affect gait parameters by increasing cognitive load in gait experiments in healthy elderly and PD patients experiencing FOG. The AST did not affect FOG severity in PD patients. An interaction effect between cognitive load and visual cues was found for stride length. Interaction effects for velocity, cadence, stride time, and stride length coefficient of variation were inconsistent in our study and require replication to assess their validity. Nevertheless, interaction effects

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should be considered in studies investigating cognitive load and visual cues simultaneously.

Abbreviations

AST, auditory Stroop task; AST_high, high load version of the auditory Stroop task; AST_low, low load version of the auditory Stroop task; FAB, Frontal Assessment Battery; FOG, freezing of gait; MMSE, mini-mental state examination; N-FOGQ, New Freezing of Gait Questionnaire; PD, Parkinson's disease; RNT, random numbers task; RNT_high, high load version of the random numbers task; RNT_low, low load version of the random numbers task; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III (motor examination); UPDRS-PIGD, Unified Parkinson's Disease Rating Scale (postural instability and gait disorder).

Supplementary material

Supplementary tables are available through the published, online, version of the article (doi: 10.1371/journal.pone.0220735; https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220735#se c026).

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CHAPTER 10

VISUAL CUEING VIRTUAL ENVIRONMENT PARADIGM

VISUAL CUES ADDED TO A VIRTUAL ENVIRONMENT PARADIGM DO NOT IMPROVE MOTOR ARRESTS IN PARKINSON'S DISEASE

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Abstract

Background: Elucidating how cueing alleviates Freezing of Gait (FOG) in Parkinson's disease (PD) would enable the development of more effective, personalized cueing strategies. Here, we aimed to validate a visual cueing virtual environment (VE) paradigm for future use in e.g. neuroimaging studies and behavioural studies on motor timing and scaling in PD patients with FOG.

Methods: We included 15 PD patients with FOG and 16 age-matched healthy controls. Supine participants were confronted with a VE environment displaying either no cues, bars or staircases. They navigated forward using alternate suppression of foot pedals. Motor arrests (as proxy for FOG), and measures of motor timing and scaling were compared across the three VE conditions for both groups.

Results: VE cues (bars and staircases) did not reduce motor arrests in PD patients and healthy controls. The VE cues did reduce pedal amplitude in healthy controls, without effects on other motor parameters.

Conclusions: We could not validate a visual cueing VE paradigm to study FOG. The VE cues possibly failed to convey the necessary spatial and temporal information to support motor timing and scaling. We discuss avenues for future research.

Trial registration: This study was registered in the Dutch trial registry (NTR6409; 2017-02-16; https://www.trialregister.nl/trial/6229).

Background

One of the most disturbing motor symptoms of Parkinson's disease (PD) is freezing of gait (FOG), defined as a 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' (1). Freezing is not restricted to gait and can also occur in speech (2), upper limb (3) and alternate foot movements (4). Gait initiation, approaching doorways and cognitive dual tasks can trigger FOG (1). Conversely, external stimuli called 'cues', such as transverse bars on the floor or the sound of a metronome, can reduce FOG and facilitate gait initiation and continuation (5).

Different mechanisms may explain the beneficial effects of external cues. First, external cues shift automatized (affected) movements to goal-directed (preserved) movements (6). Second, cues might attract attention to the task at hand (7). Third, visual cues deliver spatial information aiding in the scaling of movement (8, 9). Fourth, auditory cues can restore motor timing dysrhythmia (5, 9, 10). Lastly, external cues can improve anticipatory postural adjustments (APAs) preparing for step initiation (5). Despite the wealth of hypotheses on the mechanisms underlying externally cued gait in PD, their neurophysiological grounds await to be unveiled (5). Patients respond heterogeneously to the various cueing modalities (11, 12) – e.g. some patients profit mostly from visual cues while others respond better to auditory cues – suggesting that different neurophysiological pathways are involved. Elucidating the neuronal pathways that 'bypass' or modify defective pathways would enable a mechanistic and hypothesis-driven rather than trial-and-error based development of personalized cueing strategies.

To date, neuronal structures involved in externally cued movement have been studied in healthy persons (13, 14), to a lesser extent in PD patients (15-17), and rarely in PD patients with FOG (18, 19). Considering the structural and functional cerebral changes in PD patients with FOG, the findings in healthy individuals and PD patients without FOG cannot necessarily be extrapolated to PD patients with FOG.

A validated paradigm to study visually cued lower limb movement in a neuroimaging study is not yet available. Virtual environment (VE) paradigms

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can be useful to study FOG (4, 20-25). Specifically, participants navigated through a VE environment using alternate depression of foot pedals. Motor arrests occurring during foot pedalling were considered equivalents of FOG episodes. Functional magnetic resonance imaging studies that employed this VE paradigm provided relevant insights into the pathophysiology of FOG (22, 25). By incorporating visual cues into the VE environment, this paradigm could serve to study the neurophysiological mechanisms involved in visual cueing, and to investigate motor timing and scaling in PD patients with FOG.

In this study, we aimed to validate a visual cueing VE paradigm for use in future neuroimaging studies and behavioral studies on motor timing and scaling in PD patients with FOG. Our objectives were to assess: (1) whether visual cues in VE altered measures of motor arrests (as a proxy for freezing severity); (2) whether these VE cues altered motor timing and scaling; and (3) whether the effects of VE cues were different between PD patients and healthy controls. We hypothesized that VE visual cues would reduce the percent time spent on motor arrests, and the number and duration of motor arrests; improve motor timing by increasing step time, and reducing step time variability, cadence, and start latency; and improve amplitude generation by increasing pedal amplitude and reducing its variability. These effects were expected to be larger in PD patients than in healthy controls.

Methods and Materials

Participant selection

We included 20 PD patients and 16 age-matched healthy controls (Table 1). Inclusion criteria for patients were a diagnosis of PD according to the UK Brain bank criteria (26), and a subjective experience of FOG episodes more than once per day. Exclusion criteria included: significant cognitive impairment (mini mental state examination score [MMSE] ≤24 or frontal assessment battery [FAB] score ≤8); comorbidity causing severe gait impairments; inability to lie supine for the duration of the experiment; and severe visual impairments precluding the participant from seeing the VE cues. PD patients were tested 'Off' medication after overnight withdrawal of dopaminergic medication (>12 hours after last intake). This is important because previous

studies employing the VE paradigm found that freezing-related features are more prominent during 'Off' states compared to 'On' states (21, 23). Patients fulfilled the following clinical assessments: New Freezing of Gait Questionnaire (NFOG-Q) (27), MDS-UPDRS part III (28), MMSE (29) and FAB (30).

Virtual Environment experimental set-up

Participants were positioned lying on their backs, the knees slightly bent, and the feet on foot pedals (Figure 1A). A tablet computer (surface pro 4, Microsoft) displayed a three-dimensional VE environment from a first-person perspective, built with the game engine Unity (version 5, Unity Technologies) in combination with Visual Studio (2015, Microsoft) for script editing.

The VE environment resembled a corridor (width 4m, height 4m) with plain white walls, a grey carpet on the floor, unobtrusive objects like plants and furniture at irregular distances, and wide doorways every 20m (except in the staircase condition). In the control condition, no visual cues were displayed (Figure 1B). The experimental VE cueing conditions displayed either regularly spaced white transverse bars (width 0.9m) at 40% of the participant's height (Figure 1C), or a staircase (width 0.9m) every 25 meters (Figure 1D). Pedal angles were converted to voltages by flex sensors (4.5", Antratek) attached under each foot pedal. An Arduino-based single-board microcontroller converted these signals from analog to digital and determined the position and direction of the pedal movements. Custom software on the tablet computer received the order and speed of pedal depressions, and translated these into a corresponding change in forward progression through the VE environment in real-time. Alternate pedal depressions lead to forward progression while non-alternate stepping (e.g. left – left) did not. Pedal data were stored for post hoc signal analysis.

An auditory Stroop task (31) was applied in all trials to increase cognitive load and induce freezing-related motor alterations. The Stroop task consisted of congruent word pairings (a male voice saying 'man', or a female voice saying 'woman') signalling the participant to stop walking / pedalling ('STOP'), and incongruent word pairings (a male voice saying 'woman' or vice versa)

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signalling to start or resume walking / pedalling ('WALK'). These Stroop signals were clustered into three different 'Stroop events': (1) a single WALK; and paired signals with (2) a WALK, or (3) STOP followed within 1 to 4 seconds by a WALK. Per trial, three to four Stroop events occurred at random time intervals of which at least one was a paired STOP/WALK event.

The VE experiment was divided into a training session and 6 experimental sessions. Each experimental session was subdivided into two blocks, each consisting of three randomly ordered trials under one of the three cueing conditions. Each trial lasted 30 seconds, with its start and end indicated by a voice record saying 'start' and 'stop'.

Table 1 Clinimetrics

	PD patients Median [Q1-Q3]	Healthy controls Median [Q1-Q3]	p-value
Number of participants*	15	16	
Age (years)	71 [62,5 - 73]	68 [65,5 - 70,5]	0,251
Gender (% male)	87	44	0,015
Disease duration (years)	11 [7,5 - 17,8]		
Years since FOG	4 [2,3 - 6,8]		
LEDD (mg/day)	1130 [1002 - 1324]		
UPDRS-part III	39 [30,3 - 47]		
Hoehn and Yahr (II / III)	10 / 5		
MMSE	29 [27,3 - 30]		
NFOGQ	20 [16 - 23]		
FAB	16 [14,3 - 17]		

The median and first (Q1) and third (Q3) quartiles are given, unless stated otherwise. A p-value < 0.05 indicates a significant difference between PD patients and healthy controls. * Number of valid participants, not including five PD patients who were excluded from analyses because of insufficient signal quality. PD, Parkinson's disease; FOG, freezing of gait; LEDD, levodopa equivalent daily dose; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III; MMSE, mini-mental state examination (range 0–30); N-FOGQ, New Freezing of Gait Questionnaire (range 0–28); FAB, Frontal Assessment Battery (range 0–18). All questionnaires were rated while participants were OFF medication.
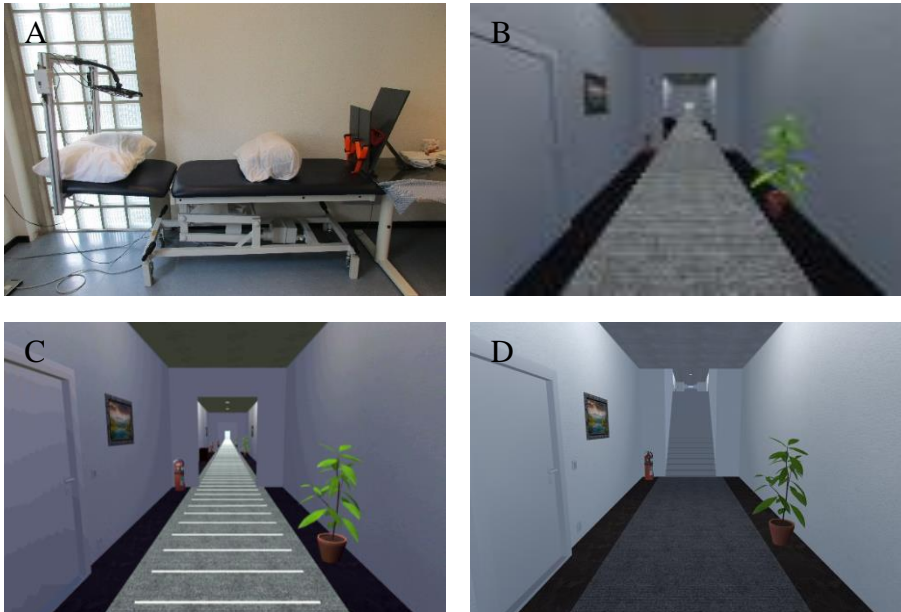
Figure 1. Virtual Environment experimental set-up

Experimental set-up (A) in which participants were lying supine with the knees slightly bend and the feet on foot pedals. The alternate suppression of the foot pedals led to a forward movement through a virtual environment (VE) displayed on a screen in front of their faces. The VE consisted of a corridor with either (B) no visual cues, (C) transverse bars, or (D) staircases.

Signal pre-processing

The pedal angle signals were resampled at 50 Hz. A sliding window of 2.5 s and an overlap of 25% was applied. The signals from both feet were normalized per window by subtracting their means. Positive and negative peaks were detected as the maximum absolute amplitudes. Peaks were removed in two subsequent runs if they 1) occurred in a time frame without crossing of the signals from the left and right foot lasting either a) > 2 seconds (first run), or b) > 2 times the median time interval between two alternate valid peaks (second run); 2) co-occurred within 3 samples of a peak of the opposite foot ('in phase', typical of noise); 3) had an amplitude < 30% of the median amplitude, and/or a peak width ≤ 5 samples (i.e. ≤ 0.1 s); or 4) occurred in sequence with a higher peak from the same foot. If over 75% of detected peaks were removed, data were

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considered of insufficient quality and the trial was marked invalid. Participants were excluded from analyses if more than half of the trials in at least one condition were invalid. 'Footstep latency' (FSL) was defined as the temporal interval between two alternate (e.g. left - right) valid peaks. A threshold calculated as 2 times the median FSL (mFSL) was used to differentiate 'walking' from 'standing still'. The 'standing still' episodes were further differentiated into 1) 'trial initiation', from the start of the trial until the first step or passing 3 sec, 2) 'trial hesitation', continuation of standing still after trial initiation, 3) 'intended stand still', standing still occurring between a stop signal until 3 sec after the successive start signal, 4) 'triggered unintended stand still', standing still following within 3 sec from a start cue, 5) 'start hesitation', continuation of standing still after an intended or triggered unintended stand still, and 6) 'spontaneous unintended stand still', standing still not following a stop nor start cue (additional figure 1). Trial hesitations, start hesitations and spontaneous unintended stand stills were considered 'motor arrests'. Parameters for motor timing and scaling were calculated over the 'walking' episodes.

Study parameters

Measures of freezing severity were: percentage of time in a trial spent on motor arrests, and mean number and duration of motor arrests per trial. Parameters for motor timing and scaling were cadence, step time, step time coefficient of variation (COV), pedal amplitude, pedal amplitude COV, and latency to start walking after an intended stand still (as equivalent to gait initiation).

Statistical analysis

All data analyses were performed with MATLAB R2017b (Mathworks, Inc., Natick, MA, USA; statistics toolbox installed). Alpha was set at 0.05 unless stated otherwise, and adjusted with the Bonferroni-Holmes method for post hoc planned comparisons. Normality of distributions was assessed by visual inspection of histograms and Q-Q plots, and tested by Shapiro-Wilk tests. Motor arrest parameters were not normally distributed regardless of transformations which were therefore not applied. Interactions between cues and participant class were not assessed for motor arrest parameters due to the unavailability of a suitable non-parametric test. Motor arrest parameters were

tested with the Friedman test and post hoc Wilcoxon-signed rank tests for the effect of cues (within-factor) per category of the participant class, and with the Mann-Whitney U test for the effect of participant class (between-factor) per category of cues. Parameters for motor timing and scaling were normally distributed. Interactions between cues and participant class were assessed with a two-way mixed ANOVA (within-factor 'cues'; between-factor 'participant class'). In the presence of outliers (defined as values outside 1.5*interquartile range (IQR) below the first or above the third quartile), the analyses were repeated without outliers and reported if this changed statistical significance. Homogeneity of variances was assessed by Levene's test, homogeneity of covariances (alpha 0.001) with the Box's M test. If Mauchly's test indicated that the assumption of sphericity was violated, p-values were corrected with epsilon calculated according to Greenhouse & Geisser. The effects of cues on motor timing and scaling parameters were analysed with one-way repeated measures ANOVAs and post hoc paired t-tests, either per category of participant class (in the presence of an interaction), or for both participant classes together (in the absence of an interaction). The effects of participant class were tested with one-way ANOVAs, either per category of cues (in the presence of an interaction) or for all cues together (in the absence of an interaction). Clinimetrics were compared with Mann-Whitney U tests and Fisher's exact tests.

Results

Data of 5 out of 20 PD patients, but none of the controls, were excluded from analyses because of low signal quality. Their clinimetrics did not differ significantly from the PD patients included for analyses.

Effects of VE cues on motor arrest severity

Neither the VE bars nor staircase condition significantly changed the percentage of time spent on motor arrests, and the number and duration of motor arrests, compared to the control condition in both PD patients and controls (Figure 2).

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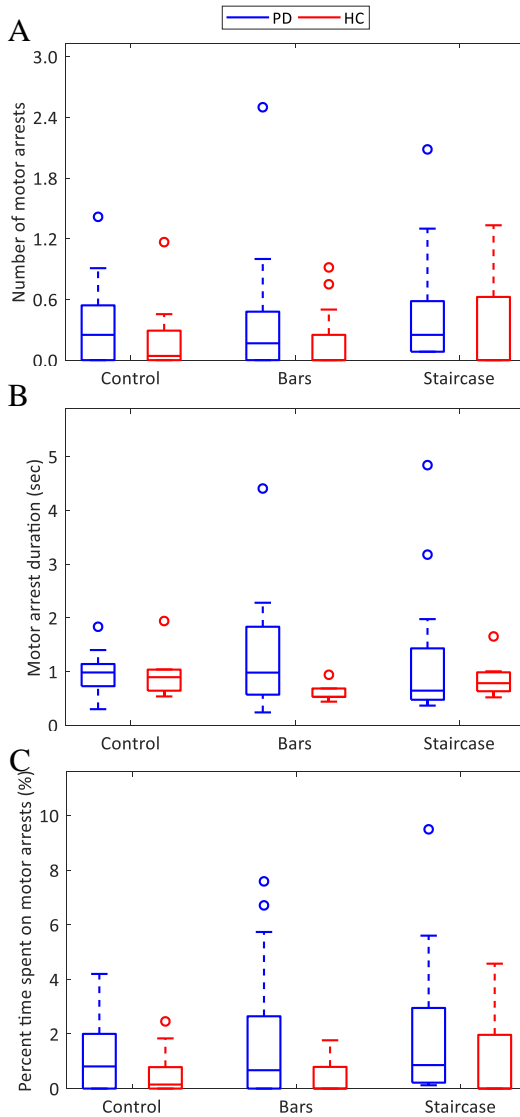
Figure 2. Effects of VE cues on motor arrest severity

Boxplots showing the mean number of motor arrests (A), duration of motor arrests (B) and percentage of time spent on motor arrests (C) in the VE cueing conditions without cues ('Control'), and with bars ('Bars') or staircases ('Staircase'). In the absence of significant effects of the VE bars and staircase conditions compared to the control condition, no significance marks are present in the plots.

Effects of VE cues on motor timing and scaling

Both the VE bars and staircase reduced pedal amplitude compared to the control condition in healthy subjects (Figure 3). Other motor timing and scaling parameters were not significantly different amongst conditions. If outliers were excluded, there was an additional increase in pedal amplitude COV in the staircase versus control condition (participant groups combined).

PD patients versus controls

The assumptions of homogeneity of variances and covariances were violated for pedal amplitude COV and start latency. When outliers were excluded, the assumption of homogeneity of variances was violated for start latency.

PD patients experienced a significantly higher number of motor arrests (p<0.01), greater percentage of time spent on motor arrests (p<0.01), and higher pedal amplitude COV (p=0.03), and a lower pedal amplitude (p<0.01) than controls (Figure 2 and 3).

An interaction between cues and participant class was present for pedal amplitude ($F(2,58) = 3.99$, p 0.032), although not if outliers (one healthy control with high pedal amplitudes in each cueing condition) were excluded ($F(2,58) = 3.28$, p 0.057). The decrease in pedal amplitude caused by the bars and staircase seen in healthy controls was not present in PD patients.
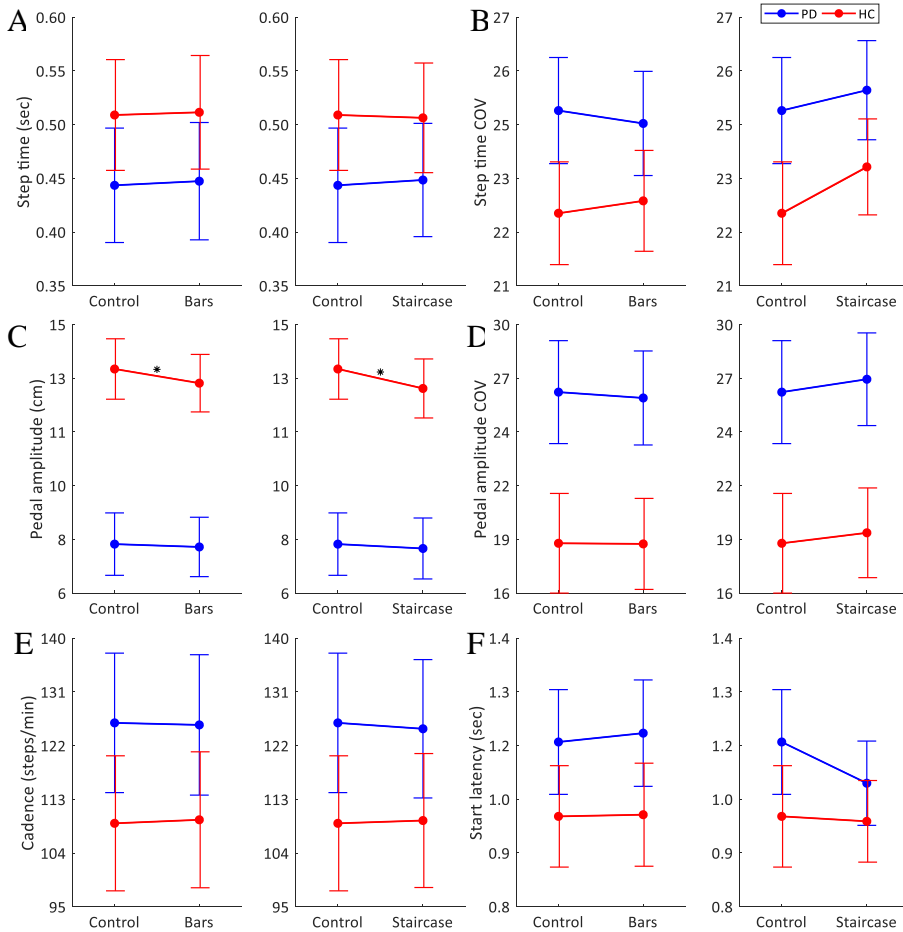
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Figure 3. Effects of VE cues on motor timing and scaling.
Profile plots showing the group mean (●) and standard error of the mean (vertical bars) for step time (A), step time coefficient of variation (B), pedal amplitude (C), pedal amplitude coefficient of variation (D), cadence (E), and start latency (F) in the different VE cueing conditions in PD patients (blue) and healthy controls (red). The control condition is compared to the bars condition (left subplots) and the staircase condition (right subplots). A significant interaction between cues and participant class is present for pedal amplitude and recognizable as the convergence between the red and blue lines in both subplots. Asterisks next to a colored line indicate a statistically significant (p<0.05) contrast within the specific participant group. Significant differences between conditions with fused participant groups (i.e. in the absence of an interaction effect) were not present.

Discussion

We aimed to validate a VE paradigm to enable future neuroimaging studies of visual cueing in patients with PD and FOG. Measures of motor arrests (as a proxy for FOG), and motor timing and scaling were compared between a control condition without cues, and across two experimental VE cueing conditions ('bars' and 'staircase'), in both PD patients with FOG and healthy controls. In contrast to our hypotheses, we found that VE visual cues gave no improvements in motor arrest severity or motor timing and scaling in patients and controls. We discuss several considerations with regard to this lack of effectivity.

First, the VE cues may not have conveyed the necessary information required to facilitate the scaling and timing of foot pedalling. The spatial information provided by the VE cues might have been perceived as unrelated to the foot pedalling movements. That the velocity of foot pedalling steered the forward movement through the VE environment with a tolerance of two footstep latencies (to prevent a jerky view), might have disrupted the perception of visual bars moving in direct response to pedal movements. A recent study employing visual cues in VE presented footprints at a pre-specified distance to provide spatial information, and changed the colour of the footprints in response to foot placement to deliver temporal information (32). An integration of footstep projections in the VE environment representing the current positions of the feet in response to the foot pedal movements, could enforce the perceived coupling between foot pedalling and walking through the VE environment.

Second, the VE cues were, in hindsight, perhaps ill chosen. Indeed, a previous study found that augmented reality bars or staircases did not improve FOG and gait, although this was perhaps attributable to the bulky smart glasses that distracted subjects from the walking task (33). However, in real life, transverse bars on the floor (34, 35), climbing staircases (36, 37) and passing a painted staircase illusion (38) were effective in improving FOG. An augmented reality tiled floor increased gait velocity and stride length in PD patients (39, 40) and FOG (41), although effects on the FOGQ were marginal and not significant for freezing frequency (41). Considering that VE tiles provide similar spatial

information to VE bars or staircases, we do not expect those to be more effective.

Third, the calculation of the parameters might have influenced the ability to measure effects. In our definition of motor arrests, unintended stand stills triggered by cognitive stimuli were not included. According to current insights, cognitive tasks can overload the neural conflict resolution capacity leading to freezing (42). Therefore, stand stills triggered by the cognitive task might be mediated by the same neural pathways as freezes during gait. Alternatively, however, a stand still following a Stroop-stimulus could be erroneous, hence being more informative about cognitive performance than the mechanisms underlying freezing. Furthermore, we based step time and its COV on the *median*, instead of the previously reported *modal* (4, 21-24, 43-45), footstep latencies. However, unlike previous studies, we differentiated 'walking' from 'standing still' prior to calculating footstep latencies in the 'walking' epochs. The footstep latencies were therefore not susceptible to skewing by motor arrests, allowing for the use of the more common median instead of the modus.

Fourth, displaying the VE environment through a virtual reality (VR)-headset rather than a screen might provide a more immersive experience, although a VR-headset would raise issues with compatibility in neuroimaging studies. Fifth, participants might not have looked at the VE visual cues with full attention, as they were not specifically instructed to do so. A recent study investigating cycling in a VE on a stationary bike showed that PD patients only increased their motor output when explicitly instructed to attend to the VE visual cues (46). Sixth, participants might have been unresponsive to visual cues in general. Certainly, PD patients vary in their responses to cues (11). We did not select participants based on their response to, or familiarity with, cues. Testing those patients with a known effect to visual cues could enhance a response to VE visual cues, to the cost of reducing generalizability of the results to PD patients with FOG without a defined response to visual cues.

Finally, since the neural circuitry underlying visual cueing has not yet been fully elucidated, it cannot be excluded that dopamine modulates the response

to visual cues. Our PD patients were tested 'Off' medication, so this could have diminished the response to cues. However, the scarce literature comparing responses to external cues during 'On' and 'Off' suggests that the effects of cues are not mediated by dopamine (47-49).

Conclusion

We were unable to validate a VE paradigm for investigating the neurophysiological mechanisms involved in visual cueing in PD patients with FOG. The original VE paradigm that we based our VE cues upon has earned its spurs in investigating the neural mechanisms underlying FOG. Adding effective visual cues to the paradigm would push a giant leap in disentangling the neurophysiological pathways mediating the effects of external cues. These insights would empower a mechanism-based development of effective cueing devices, with a final goal of improving gait in PD patients with FOG.

Abbreviations

FAB, Frontal Assessment Battery; FOG, freezing of gait; MMSE, mini-mental state examination; N-FOGQ, New Freezing of Gait Questionnaire; PD, Parkinson's disease; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III (motor examination); VE, virtual environment.

Supplementary material

Additional figure 1
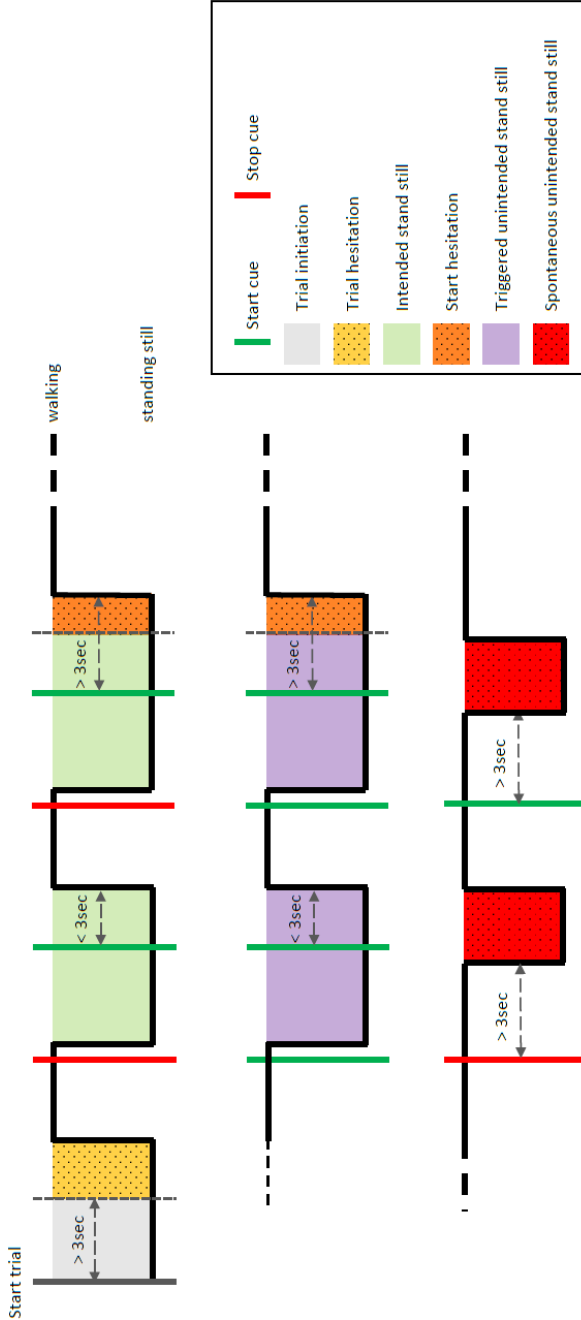
Additional figure 1. A median footstep latency (mFSL) of 2 switched states between 'walking' (upper lines) and 'standing still' (lower lines). The 'standing still' episodes were differentiated into 1) 'trial initiation' (grey), from the start of the trial until the first step or passing 3 sec, 2) 'trial hesitation' (yellow), continuation of standing still after trial initiation, 3) 'intended stand still' (green), standing still occurring between a stop signal until 3 sec after the successive start signal, 4) 'triggered unintended stand still' (purple), standing still following within 3 sec from a start cue, 5) 'start hesitation' (orange), continuation of standing still after an intended or triggered unintended stand still, and 6) 'spontaneous unintended stand still' (red), standing still not following a stop nor start cue. Trial hesitations, start hesitations and spontaneous unintended stand stills were considered 'motor arrests' (dotted pattern).

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PART IV

SUMMARY

AND

DISCUSSION

CHAPTER 11

SUMMARY AND DISCUSSION

The overarching aim of this thesis was to explore whether visual cues delivered through augmented reality glasses improve FOG and gait in persons with PD. The thesis commenced with overviews of the position of cueing as a neurorehabilitation strategy in PD, and of visual and ocular disorders that should be considered when developing visual cues. Next, I reported two intriguing cases that pointed out how heterogeneous cueing strategies can be. Then, as the core of this thesis, I presented several studies which explored the effectivity of visual cues delivered through augmented reality glasses to alleviate FOG and improve gait in persons with PD. This was followed by a study validating a task to increase cognitive load in walking experiments. The final study investigated whether a virtual environment paradigm could be used in neuroimaging and behavioural studies involving cueing.

Below, a summary of the main findings of this thesis is provided. Next, I discuss how to interpret these findings in light of current concepts and the existing literature. This is followed by a discussion of methodological limitations of our studies. This chapter ends with a paragraph discussing future perspectives and challenges.

Summary

In **Chapter 2**, I reviewed the position of neurorehabilitation as a valuable non-pharmaceutical treatment approach to relieve motor and non-motor symptoms in persons with PD. I emphasized the role of cues to alleviate FOG and improve gait. Smart glasses were addressed as promising tools to deliver wearable, personalized, patient-tailored cues 'on demand'.

Chapter 3 provided an overview of ocular and visual disorders that are prevalent in people with PD. Six common disorders, and the effects of PD-related treatments on visual function, were discussed. Also, practical recommendations for clinical management were given. These ocular and visual disturbances should be considered when designing visual cues.

Chapter 4 described a patient who self-invented compensatory strategies to improve his gait. One unprecedented strategy was to gently press his fingers bilaterally onto his temples, thereby effectively relieving and even preventing FOG. Possibly, this act was effective by enabling him to focus at the task at hand, or by serving as a single external somatosensory cue to facilitate gait initiation.

In **Chapter 5**, I presented a person with PD who experienced a striking relief of his FOG when he walked across the three-dimensional painting of a staircase on the floor. This intriguing case disclosed that the *illusion* of visual cues is sufficient to convey their effects.

Extrapolating the findings of **Chapter 5**, we hypothesized that visual cues presented in an augmented reality could be effective in reducing FOG and improving gait. Therefore, in **Chapter 6**, we explored the usability of augmented reality cues displayed via smart glasses to improve FOG and gait in persons with PD. In laboratory experiments, 25 persons with PD and FOG performed walking tasks while wearing custom-made smart glasses. Two experimental conditions (three-dimensional transverse bars and staircases displayed in augmented reality) were compared with three control conditions (conventional transverse bars, a metronome, and no cues). The number of FOG episodes and the percentage of time spent on FOG were not statistically

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different across the conditions. We attributed the lack of effects to possible distraction by the fairly bulky smart glasses, blockage of visual feedback by the frame of the smart glasses, insufficient familiarization with the smart glasses, or the display of the visual cues in the central rather than peripheral visual field. We recommended the future use of more lightweight, comfortable, and user-friendly smart glasses to avoid distraction and blockage of sensory feedback.

A remarkable finding of **Chapter 6** was not only that augmented reality cues did not improve FOG, neither did conventional cues. A possible explanation was that the wearing of smart glasses caused distraction, thereby deteriorating FOG and cancelling out the beneficial effects of cues. These hypotheses were tested in **Chapter 7**. In a single patient experiment, a person with PD who was known to be responsive to cueing performed a walking task under various cueing conditions, with and without wearing smart glasses. We found that wearing smart glasses did not worsen his FOG, nor did it affect the beneficial effects of conventional cues. Based on this report, the use of smart glasses should not be discouraged based on a fear for deteriorating FOG and counteracting the effects of cues.

The visual cues applied in **Chapter 6 & 7** were aimed at supporting straight-path walking, while most FOG episodes (both in our studies and at home) occur during turning movements. Therefore, in **Chapter 8**, we investigated whether augmented reality cues displayed through state-of-the-art smart glasses could support turning in place in persons with PD and FOG. For this purpose, we developed a novel type of visual cues, with a large sphere 'consuming' small spheres at a semi-circle around the wearer, aiming to enforce goal-directed movement. Sixteen persons with PD and FOG performed a series of 180 degree turns under an experimental condition with augmented reality visual cues displayed through smart glasses, and control conditions with a metronome and no cues. Augmented reality visual cues did not improve the percent time frozen, nor the number and duration of FOG episodes compared to the control condition without cues. Furthermore, the augmented reality visual cues impaired axial kinematics, turn scaling and timing compared to the metronome and no cues. We concluded that

stimulating goal-directed turning is by itself insufficient to improve FOG and turning performance.

Although prevalent and troublesome in the home situation, FOG is notoriously difficult to provoke in a laboratory setting. In **Chapter 9**, we validated the Auditory Stroop Task to increase cognitive load during walking tasks with a simultaneously application of visual cues. In a first experiment, 19 healthy elderly subjects performed a walking task under experimental conditions with a high and low load version of the Auditory Stroop Task, and control conditions with an alternative cognitive load task, and no additional cognitive load. In a second experiment, 20 persons with PD and FOG and 18 healthy controls performed walking tasks under the high-load version of the Auditory Stroop Task, and no additional cognitive load as control condition. Both experiments were performed with and without visual cues. We found that, compared to the control conditions, the Auditory Stroop Task negatively affected all gait parameters in both patients and controls. However, the Auditory Stroop Task did not increase the occurrence of FOG in persons with PD. Visual cues reduced the decline in stride length induced by cognitive load in both groups. We concluded that the Auditory Stroop Task is well-suited to simulate the effects of cognitive load on gait parameters, but not FOG severity, in gait experiments involving visual cueing in persons with PD and FOG.

Surprisingly, the neurophysiological pathways mediating the effects of visual cues have received little attention in research and are largely unknown. In **Chapter 10**, we aimed to validate a visual cueing virtual environment paradigm for future use in neuroimaging and behavioural studies on motor timing and scaling in persons with PD and FOG. In this experiment, supine participants (15 persons with PD and FOG and 16 healthy controls) navigated through a virtual environment by alternately suppressing foot pedals. In the virtual environment, either no cues, transverse bars or staircases were displayed. We found that neither of the virtual environment cues reduced motor arrests (as a proxy for FOG) in patients and controls. The virtual environment cues reduced pedal amplitude in healthy controls, without effects on other motor scaling and timing parameters. Possibly, the virtual environment cues failed to convey the necessary spatial and temporal

information necessary to support motor timing and scaling. We concluded that the current visual reality paradigm cannot be used to study FOG.

In short, this thesis explored whether augmented reality visual cues delivered through smart glasses could improve FOG and gait in persons with PD. Various types of visual cues and augmented reality glasses were tested. Unfortunately, none proved sufficiently effective in improving FOG and gait.

Discussion

Ways to increase a patient's benefit from cues

As discussed in **Chapter 2**, cueing strategies encompass an established non-pharmaceutical method to overcome gait difficulties in persons with PD and FOG. The actual use of cues in daily life by persons with PD and FOG has not been systemically mapped in the scientific literature. My personal clinical experience, and contacts with the participants in our studies, give the impression that the benefits of cues are not exploited to their full potential. Many patients do not use cues, either because they are not aware of their existence, have not experienced any benefits of cues, or find cues hard to use in daily life. How these three aspects can be tackled, is discussed consecutively in the next set of paragraphs.

Patient education would help to enhance patients' knowledge of the existence and potential benefit of cues. Physiotherapists and occupational therapists who are experienced with PD, FOG, and cueing can provide patients with information, tailor treatment to their individual situation, and train patients to effectively and safely make use of cues (1-4). In this regard, it is important that therapists have received additional PD-specific training according to the latest guidelines, and that they treat large numbers of persons with PD to allow them to learn from the heterogeneity across patients (4-7). Indeed, specialised therapists achieve better outcomes than generally trained therapists (6).

A patient's benefit from cues could be enhanced in multiple ways. First, extending the variety of cueing strategies would enhance a patient's chance of finding a cue that best serves him or her. Second, predicting a patient's response to different cues would accelerate the selection of a suitable cueing strategy, while minimizing the effort of trying out all sorts of cues. The various subtypes and triggers of FOG have been suggested to represent distinct pathophysiological mechanisms leading to FOG (8-10), which might be linked to a response to specific cueing modalities. Confirming these hypotheses would require more detailed insights into the neural substrates of clinically distinct manifestations of FOG, elucidation of the neuronal pathways mediating the effects of the various cueing modalities, and testing in clinical

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studies. Third, the benefit of cues could be augmented by tailoring cues to the preferences and needs of individual patients (3). One aspect to consider is that sensory deficits are common in persons with PD (11-15). Visual cues are unlikely to be effective in the presence of visual and ocular disturbances (as outlined in **Chapter 3**), just as hearing disabilities would prohibit the effectivity of auditory cues, while tactile cues would be ill-chosen in patients with gnostic sensory changes.

The usability of cues in daily practice would benefit from cueing devices that are wearable, inconspicuous, and easy to handle (**Chapter 3**) (16). The shift from stationary cues towards wearable cueing devices is ongoing (17-20). Indeed, most cueing devices currently under development - e.g. smart glasses ((19, 21), **Chapter 6, 7 & 8**), laser shoes (18, 22) and vibrating insoles (23) – are wearable. Furthermore, to be useful in daily life, cueing devices would ideally be designed as non-obtrusive gait assistants. Being rather bulky and prominent, the current augmented reality glasses have not yet reached this stage. But, at the current pace of technological development, it could become possible to integrate augmented reality into regular fit glasses within the foreseeable future. In addition, given that persons with PD and FOG often show executive dysfunction (24-26), it is of utmost importance that cueing devices are designed to be intuitive and easy to use. In the studies in this thesis, the augmented reality glasses were handled by the researchers. Whether persons with PD are capable of operating augmented reality glasses would require further study.

Reasons for the lack of effects of augmented reality visual cues

The overarching research question of this thesis was whether wearable visual cues delivered through augmented reality glasses could improve FOG and gait in persons with PD. The studies described in **Chapters 6**, **7**, & **8** consistently led to a negative answer to this question. The interpretation of this finding is less clear-cut. On the one hand, this could mean that augmented reality cues are not effective in reducing FOG and improving gait. On the other hand, this could implicate that adjustments to the augmented reality cues and cueing device are required to render them effective. Both interpretations are discussed next.

'Augmented reality cues are not effective in reducing FOG'

Given that there is only little proof of the contrary (21, 27, 28), it could be true that augmented reality cues are not effective in reducing FOG and improving gait in persons with PD.

One possible explanation could be that the simultaneous exposure to both the real environment and an augmented reality environment is too complex for patients. How exactly the human brain handles the perception of an augmented reality is unknown. Possibly, the images of the real and augmented environment are being viewed at the same time, and then merged into a single representation. Persons with PD and FOG experience difficulties in dual tasking (29, 30), rendering the simultaneous perception of two realities potentially troublesome. Alternatively, rather than merging the views of two realities into one perception, one might merely rapidly switch attention between the two realities. The executive dysfunction present in many persons with PD and FOG has shown to specifically affect attentional set-shifting, i.e. the ability to rapidly alter the focus of attention (26, 31). When attention is fixed on the real environment, one misses out on the supportive information in the augmented reality. If attention is set on the augmented reality, one could fail to perceive the environmental information that is necessary for safe ambulation.

Another possible explanation for the lack of effect of augmented reality visual cues is that the visual cues are (possibly subconsciously) judged as 'unreal' and are hence discarded. However, many cues, including the optical staircase illusion in **Chapter 5** or the laser lines projected onto the floor (18, 19, 32-34), are not a natural part of the environment, yet have proven to be effective. Therefore, that cues should be part of the normal reality to be effective, is not very likely.

'Augmented reality cues need adjustments to effectively reduce FOG'

An alternative interpretation of the findings in **Chapters 6**, **7 & 8**, showing that augmented reality visual cues did not improve FOG and hypokinetic gait, is that the cues in the specific form as they were currently designed and delivered were not effective. After all, 'no evidence of an effect', is not equal to

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'evidence of no effect' (35). Certain aspects in the delivery and design of the augmented reality cues in our studies might have precluded beneficial effects, and adjustments might render augmented reality visual cues more effective. Considerations regarding the delivery and design of the cues are discussed next.

A major drawback of the augmented reality glasses in our studies was their limited field of view. The custom-made smart glasses used in **Chapter 6** were equipped with tiltable displays, enabling projection of the augmented reality cues fairly close to the feet. However, tilting the displays sufficiently to proximate the cues to the feet cut off the upper visual field, thereby restricting visual feedback and possibly worsening FOG (29). Also, even with the displays maximally tilted, the augmented reality cues were displayed in front of the patient's feet, and it was not possible to step over the cues. The specific smart glasses used in **Chapter 7 & 8** had a fixed display in the central visual field. This caused the augmented reality bars in **Chapter 7** to start at one to a few meters away from the feet, depending on the degree of anteflexion of the neck. Unless the neck was unnaturally flexed, the patient could not step over the augmented reality bars, and instead rather walked towards the bars which would then disappear upon approaching. Upcoming generations of augmented reality glasses are expected to provide a wider field of view. In fact, the recently released successor of the smart glasses used in **Chapter 7 & 8** already does. Whether this wider field of view is sufficient to deliver augmented reality bars one could step over, remains to be determined.

Another point of concern is that the augmented reality glasses, which were rather bulky and heavy, could have caused a distraction of attention. As previously discussed, persons with PD and FOG often exhibit problems with dual tasking (29, 30). Distraction by the glasses could have deteriorated FOG and gait, and counteracted a potential beneficial effect of cues. We tested these specific hypotheses in a single patient study (**Chapter 7**), and found no worsening of FOG and gait, or cancelling out of the effects of conventional cues, when augmented reality glasses were worn. Even though these findings are reassuring, confirmation in a larger cohort obviously remains required.

Another factor which might have impeded the effectivity of the augmented reality cues is that all patients within a study were exposed to the same cues. In clinical practice, it is recognized that patients show a differential response to the various cueing modalities and types of cues (3). Patients with a known response to conventional visual cues are more likely to also respond to augmented reality visual cues. However, selecting the patients with a known response to visual cues would be challenging, as for many patients their responses to various cues are unknown. Also, such selection would impede the inclusion of sufficient patient numbers, and reduce the generalizability of the results. Furthermore, even within a cueing modality, patients often have personal preferences regarding the design of the cues (3). Except for the distances between the augmented reality transverse bars, which were adjusted for participant height in **Chapter 6**, no subject specific adjustments to the cues were made. Intuitively, it seems likely that taking patient preferences into account, for example with regard to the shape (36, 37), color (38), size (37) and frequency of cues (39), would enhance the effectivity of cues. Again, this requires confirmation in clinical studies.

Furthermore, the augmented reality cues in our studies did not provide feedback about the actual performance of the walking task. The field of view issues discussed earlier prohibited placement of the feet between the augmented reality bars in **Chapter 6 & 7**, restraining visual feedback of the correct spacing of the steps. This lack of feedback might have provided too little incentive and support to adjust the scaling of movement, which is thought to be an important working mechanism of visual cues (20, 40). If the field of view issues cannot be resolved, it could be an option to display a representation of the feet, or an avatar, in the augmented reality environment, providing information on the scaling of movement with regard to the augmented reality cues.

A possibility to consider, is that patients might not have adjusted their walking and turning with the information provided by the cues. In fact, it was possible for a patient to fully ignore the visual cues, without experiencing any negative consequences. This is different for real transverse bars on the floor, which would cause the patient to trip over if the bars were not paid attention to.

Three-dimensional bars on the floor stimulate a person to lift the feet higher, thereby possibly activating a different, possibly better preserved, motor program compared with normal walking (36). However, many conventional cues, including laser lines (19, 32, 41) or lines taped onto the floor (42), are effective without any repercussion if ignored. Also, the participants in our studies gave a convincing impression to try and make use of the cues that were provided to them.

A last possible explanation for the lack of results of the augmented reality cues, is that participants were insufficiently trained to exploit the cues optimally. Previous research often provided repeated cueing training along the course of several weeks (32, 43-45), although other studies found effects of cues even after a single evaluation (22, 38, 46, 47). However, the patients in our study were in general not accustomed to virtual or augmented reality displays (e.g. in **Chapter 8**, two-thirds of patients had never seen an augmented or a virtual reality before), which might have necessitated extended training to sufficiently familiarize patients with the augmented reality cues.

Development of novel cueing strategies

The development of cueing strategies was originally based on the extension of clinical observations in individual patients to assessments in larger patient cohorts. Here, the inventiveness of patients, attentiveness of healthcare workers, and dedication of researchers are as beads of a chain. If any of the beads is missing, for example if the discovery of a novel cue by an individual patient does not reach the attention of dedicated researchers, the chain of developing a novel cueing strategy would be broken. Therefore, although the inventiveness of patients in discovering novel cueing strategies remains vital input to research (as highlighted in **Chapter 4 & 5**), this method is bound to be rather slow and inefficient.

An analysis of existing cueing strategies has led to the position of various hypotheses on the working mechanisms of cues (20, 40). These hypotheses include a cueing-induced shift from automatized towards goal-directed behaviour, redirection of attention to gait, and support in the scaling and timing of movements (20). The current development of cueing strategies is

predominantly based on these presumed working mechanisms. This has accelerated the development of cueing strategies considerably, but does not take the underlying neurophysiology of the cueing mechanisms into account. The pathophysiological origin of FOG likely differs across patients (8-10), and a cueing strategy which bypasses the particular neuronal structure or pathway affected in an individual carries the most potential to resolve the FOG. Gaining insights into both the diverse pathophysiology of FOG and neurophysiological mechanisms underlying various cueing therapies would allow tailoring of cueing therapy to a patient's individual FOG pathophysiology, with a final goal of increasing the potency of cueing therapy.

The elucidation of the pathophysiology of FOG has received considerable attention by renowned research groups (8, 29, 48-69). On the contrary, only few studies focused on the neurophysiological grounds of cueing in persons with PD and FOG (53, 70). A complicating factor is that a validated paradigm to study visually cued lower limb movement (as a proxy for gait) in a neuroimaging study is not yet available. Unfortunately, our attempt to extend an established virtual environment paradigm (54, 55, 57, 71-75) by incorporating visual cues did not result in a validated paradigm for future use in neuroimaging studies and behavioural studies on visual cueing in persons with PD and FOG (**Chapter 10**). As discussed elaborately in the Discussion section of **Chapter 10**, the visual cues in the virtual environment apparently 'did not have what it takes' to improve movement control. However, improvements to the paradigm, such as strengthening the coupling between foot movements and the view in the virtual environment, could render the paradigm better suited for the purpose of studying the neurophysiology of cueing. Considering the value that the virtual environment paradigm has had in the study of the pathophysiology of FOG (54, 55, 57, 71-75), this paradigm, if adjusted, does hold potential to study the neurophysiological grounds of visual cueing.

Limitations

An important limitation to our studies were the rather small sample sizes, and the heterogeneous nature of the participant groups. Cohorts of 15-20 patients should be sufficient to find statistically significant differences if the effect size

of the intervention is large, and if the patients are homogenous in their response to the intervention (76). In our studies, possibly neither of these requirements were met. The augmented reality visual cues were novel, and their expected effect size was estimated based on effects seen earlier for existing conventional visual cues. The effect size of augmented reality visual cues might be smaller than that of conventional cues, requiring larger participant groups to find statistical differences. Also, as previously discussed, patients differ in their response to cues (3). Because we did not select those patients with a known response to visual cues, the response to the cues was most likely heterogeneous.

Another limitation to the studies described in **Chapter 6 & 8** was that there was no control condition during which the augmented reality glasses were not worn. Including conditions both with and without wearing augmented glasses, such as in **Chapter 7**, would have allowed to control for the effects of wearing augmented reality glasses.

The studies in this thesis were all laboratory-based, while the cueing device should eventually be used in the daily life situation. Daily life poses specific challenges to applying an intervention and measuring its effects that are not present in well-controlled laboratory-based experiments (77). As effectivity of augmented reality cues had not yet been proven, we decided to focus first on demonstrating the effectivity of augmented reality cues in a controlled environment, before proceeding to testing in the home situation. This last step, however, could not be made in this thesis because of the negative results of the laboratory-based studies.

Future perspectives

Whether there is a future for augmented reality visual cues delivered through smart glasses in the treatment of FOG largely depends on forthcoming technical developments. If issues regarding the visual field and wearing comfort can be conquered, then it might be well worth reattempting to beat FOG with augmented reality cues. Subsequently, an important next step would be to test the effectivity and usability of cues delivered through augmented reality glasses in the home situation.

The usability of cues in general is likely to profit from tailoring cues to a patient's needs and preferences, for example with regard to the shape, colour, size and frequency of cues (3). In addition, ideally, it will become possible to match the cueing strategy to an individual's FOG pathophysiology.

An important forthcoming development is that of automatic detection and prediction of FOG (17, 78-83). Reliable automatic FOG detection and prediction would enable the delivery of cues during or even prior to the start of FOG episodes ('cueing-on-demand'), as well as objective identification and quantification of FOG for research and clinical purposes. Current research commonly applies machine learning techniques on movement data collected with wearable sensors to recognize FOG specific patterns (78, 83). These analyses would benefit from the installation of a central repository for the collection of large amounts of heterogeneous FOG data. In addition, the accuracy of FOG detection and prediction would be boosted by the combination of different data sources, e.g. data from motion and pressure sensors, heart rate, skin conductivity, electro encephalography and even brain metabolism.

If questioned 'Virtual visual cues: vice or virtue?', my answer is that this thesis found no support for augmented reality visual cues as a 'virtue'. This, however, does not implicate that augmented reality cues can be discarded as 'vice'. It is up to future technological developments, and research efforts, to render augmented reality visual cues viable.

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CHAPTER 12

NEDERLANDSE SAMENVATTING | SUMMARY IN DUTCH

De ziekte van Parkinson

De ziekte van Parkinson is een veelvoorkomende bewegingsstoornis. Bij de ziekte van Parkinson sterven dopamine-producerende cellen in de hersenen af. Hierdoor ontstaat een tekort aan dopamine. Dit dopamine tekort veroorzaakt een scala aan verschijnselen, waaronder traagheid, stijfheid, trillen en loopproblemen.

Bevriezen van lopen

Bij de progressie van de ziekte ervaart een meerderheid van de mensen met Parkinson 'bevriezen van lopen', in het Engels 'freezing of gait' genoemd. Bevriezen van lopen wordt wel omschreven als het gevoel 'alsof de voeten plotseling zijn vastgeplakt aan de vloer', of 'alsof je met je voeten ineens in een lijmpot staat'. Factoren die bevriezen van lopen kunnen uitlokken zijn onder andere draaien op de plaats, het passeren van een nauwe doorgang (zoals een deuropening), het uitvoeren van dubbeltaken en het ervaren van tijdsdruk. De oorzaak van bevriezen van lopen is nog niet volledig opgehelderd. Bevriezen van lopen is een uitermate vervelende klacht. Door bevriezen van lopen zijn mensen minder mobiel, hebben zij een verhoogd risico om te vallen en ervaren zij een verslechterde kwaliteit van leven.

Medicamenteuze behandeling van de ziekte van Parkinson heeft vaak maar een gering effect op bevriezen van lopen. Een alternatieve behandelstrategie is het toepassen van 'cues', oftewel het gebruiken van stimuli om in het loopritme te komen en te blijven. Cues kunnen ritmes zijn die worden gezien (zoals strepen op de vloer), gehoord (bijvoorbeeld het tikken van een metronoom) of gevoeld (zoals een trillend bandje om de pols of voet). Mensen verschillen in hun reacties op cues – de cue die bij de ene persoon effectief is hoeft bij een ander niet hetzelfde effect te hebben.

Er bestaat een behoefte aan een draagbaar hulpmiddel dat gepersonaliseerde cues kan leveren. Mogelijk dat smart glasses ('slimme brillen') hier uitkomst kunnen bieden. Met behulp van ingebouwde technologie kunnen smart glasses de werkelijkheid aanvullen met virtuele visuele informatie, in het Engels 'augmented reality' genoemd.

Doel en opbouw van dit proefschrift

In dit proefschrift onderzoek ik of visuele cues aangeboden in een augmented reality het lopen kunnen verbeteren bij mensen met Parkinson en bevriezen van lopen. Het proefschrift is onderverdeeld in drie delen. In het eerste deel beschrijven we de positie en randvoorwaarden van cueing als neuro-revalidatie strategie bij de ziekte van Parkinson. In het tweede deel beschrijven we verschillende studies waarin nieuwe, vooral visuele, cueing technieken worden onderzocht. In het derde deel worden nieuwe onderzoeksmethoden voor studies met cues onderzocht.

Deel I Positie en randvoorwaarden van cueing als neuro-revalidatie strategie bij de ziekte van Parkinson

Hoofdstuk 2 geeft een overzicht van de positie van neuro-revalidatie in de behandeling van mensen met de ziekte van Parkinson. We benadrukken hierbij de belangrijke rol van cueing strategieën bij de behandeling van bevriezen van lopen bij mensen met Parkinson. Smart glasses worden aangedragen als veelbelovende hulpmiddelen om draagbare, gepersonaliseerde cues aan te bieden.

In **Hoofdstuk 3** worden oog- en visusproblemen besproken welke vaak voorkomen bij mensen met de ziekte van Parkinson. Bij het ontwikkelen en toepassen van visuele cueing hulpmiddelen is het belangrijk om dergelijke problemen in ogenschouw te nemen.

Deel II Nieuwe cues om bevriezen van lopen te verlichten

In **Hoofdstuk 4** wordt een persoon met de ziekte van Parkinson beschreven die verlichting van bevriezen van lopen ondervindt door met de wijsvingers beiderzijds licht op de slapen te drukken.

De inventiviteit van patiënten en mantelzorgers bij het bedenken van nieuwe manieren om bevriezen van lopen te verminderen wordt verder onderstreept in **Hoofdstuk 5**. Hierin wordt een persoon met Parkinson beschreven met ernstig bevriezen van lopen die een opvallende verbetering van zijn klachten bemerkte als hij over de schildering van een trap op de vloer liep. Dit maakt

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duidelijk dat klaarblijkelijk de *illusie* van visuele cues voldoende is om effectief te zijn.

De bevinding van **Hoofdstuk 5** doortrekkend, stelden we de hypothese op dat visuele cues aangeboden in een augmented reality bevriezen van lopen zouden kunnen verminderen. Dit wordt onderzocht in **Hoofdstuk 6**. Hiertoe voerden 25 personen met Parkinson en bevriezen van lopen verschillende looptaken uit terwijl zij smart glasses droegen. Vijf verschillende condities werden vergeleken: 1) drie-dimensionele balken, en 2) een trap afgebeeld in augmented reality middels smart glasses; 3) echte balkjes op de vloer; 4) het tikken van een metronoom; en 5) geen cues. In deze studie vonden we geen verbetering van bevriezen van lopen of loopkwaliteit met de visuele cues via smart glasses. We vermoedden dat de bril voor afleiding, of een blokkade van het gezichtsveld, had gezorgd. We adviseerden om toekomstig onderzoek met lichtere, comfortabelere en gebruiksvriendelijkere smart glasses uit te voeren.

Een opmerkelijke bevinding in **Hoofdstuk 6** was dat ook de meest gangbare cues, namelijk de metronoom en echte balken op de vloer, niet effectief waren. In **Hoofdstuk 7** onderzochten we bij één persoon met Parkinson of het dragen van smart glasses het effect van cues tegenwerkte en misschien zelfs bevriezen van lopen verslechterde. Dit bleek niet het geval, het dragen van smart glasses had geen effect op bevriezen van lopen of op het effect van cues.

De voorgaande twee hoofdstukken richtten zich op rechtuit lopen. Echter, veel personen met Parkinson ervaren bevriezen van lopen juist tijdens het draaien op de plaats. In **Hoofdstuk 8** onderzochten we of visuele cues aangeboden via smart glasses het draaien op de plaats zouden kunnen verbeteren middels het stimuleren van het uitvoeren van een doelgerichte beweging. Zestien personen met Parkinson met bevriezen van lopen voerden een draaitaak uit terwijl zij een nieuw type smart glasses droegen. Het effect van de visuele cues via de smart glasses werd vergeleken met de effecten van een metronoom en de conditie waarin geen cues aanwezig waren. Ook in deze studie vonden we geen verbetering van bevriezen van lopen met de visuele cues via smart glasses. Sommige bewegingsparameters bleken zelfs te verslechteren met de visuele cues. We concludeerden dat het stimuleren van

een doelgerichte beweging onvoldoende is om bevriezen van lopen en draaien te verbeteren.

Deel III - Nieuwe onderzoeksmethoden voor studies met cues

In dit deel van de thesis verleg ik de aandacht naar het ontwikkelen van nieuwe onderzoeksmethoden voor toekomstig onderzoek naar de toepassing en effectiviteit van cues.

Het uitvoeren van dubbeltaken kan bevriezen van lopen uitlokken. In **Hoofdstuk 9** onderzochten we of een 'Auditieve Stroop Taak' het effect van dubbeltaken op lopen kon nabootsen. Ook onderzochten we wat het effect van gelijktijdige blootstelling aan de Auditieve Stroop Taak en visuele cues was. We voerden hiertoe twee experimenten uit. In het eerste experiment werd het lopen van gezonde personen vergeleken met 1) de Auditieve Stroop Taak, 2) een cognitieve controle taak, en 3) zonder cognitieve taak. De looptaken werden uitgevoerd met en zonder visuele cues. In het tweede experiment legden mensen met Parkinson en bevriezen van lopen, en gezonde controlepersonen, een looptaak af met en zonder de Auditieve Stroop Taak, en met en zonder visuele cues. In deze twee experimenten vonden we dat bij zowel controlepersonen als mensen met Parkinson het lopen verslechterde door de Auditieve Stroop Taak. De Auditieve Stroop Taak gaf geen toename van bevriezen van lopen bij mensen met Parkinson. We concludeerden dat de Auditieve Stroop Taak kan worden gebruikt om het effect van dubbeltaken op lopen te simuleren, maar niet om bevriezen van lopen uit te lokken.

In **Hoofdstuk 10** hebben we beoogd een onderzoeksmethode te valideren voor toekomstig beeldvormend onderzoek naar de werkingsmechanismen van cueing. Hiertoe maakten we gebruik van een bestaand onderzoeksprotocol, waarbij een proefpersoon door een virtuele werkelijkheid navigeert middels voetpedalen. Wij voegden visuele cues aan deze virtuele werkelijkheid toe. Vijftien personen met Parkinson en vijftien controlepersonen voerden een proef uit waarbij ze door de virtuele omgeving 'liepen', met en zonder toevoeging van visuele cues in de virtuele omgeving. In deze studie vonden we geen verbetering van de voetbewegingen van de proefpersonen. Mogelijk brachten de visuele cues in de virtuele omgeving niet de juiste informatie over

zoals echte cues dit doen. We concludeerden dat de onderzoeksmethode met visuele cues in een virtuele werkelijkheid (nog) niet kan worden gebruikt bij vervolgonderzoek.

Met dit proefschrift werd geen ondersteuning gevonden voor de hypothese dat visuele cues via een augmented reality bevriezen van lopen kunnen verbeteren bij mensen met de ziekte van Parkinson. Dit betekent niet dat dergelijke cues niet kúnnen werken. Verdere technologische ontwikkelingen en vervolgonderzoek zullen moeten uitwijzen of visuele cues via smart glasses een toekomst hebben bij de behandeling van mensen met de ziekte van Parkinson.

PART V

APPENDICES

A1.   LIST OF PUBLICATIONS

Janssen S, Ruyter de - Steveninck van J, Salim HS, Bloem BR, Heida T, Wezel van RJA. The beneficial effects of visual cues are retained when augmented reality glasses are worn. *Submitted*

Janssen S*, Ruyter de - Steveninck van J*, Salim HS, Cockx HM, Bloem BR, Heida T, Wezel van, RJA. The effects of Augmented Reality visual cues on turning in place in Parkinson's disease patients with Freezing of Gait. *Submitted*

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A3.   ABOUT THE AUTHOR

Sabine Janssen was born on July 23th 1988 in Huizen, the Netherlands. After graduating from secondary school (Valuascollege, Venlo) cum laude, she studied Medicine at the Radboud University, Nijmegen, the Netherlands. An elective clinical internship at the Neurology department at the University of Debrecen, Debrecen, Hungary, piqued her interest in neurology. A master class Neurology at the Radboud University, Nijmegen, raised her interest in research. In 2009-2010, she joined a research group led by Prof. Dr. F. Hildebrandt at the University of Michigan, Ann Arbor, United States of America. Here, she studied the genetic background of ciliopathies. She returned to the Radboud University to finish her clinical internships. Meanwhile, she assisted in research on the role of the cerebellum in dystonia, under supervision of Prof. Dr. van de Warrenburg at the Radboud University Medical Centre, Nijmegen, the Netherlands. In 2013 she finished medical school cum laude and started a specialization in Neurology at the Radboud University Medical Centre, Nijmegen. Soon, she was gripped by the complexity and versatility of neurodegenerative disorders, Parkinson's disease in particular. In 2015 she started as a PhD student in the research group of Prof. Dr. van Wezel at the University of Twente, Enschede, the Netherlands. She investigated the application of visual cues in augmented or virtual reality in Parkinson's patients with freezing of gait. The results of these studies are described in the current thesis.

Sabine is married to Raymond and they hope to welcome their first child in the spring of 2020.