Opposing gait impairments deriving from Parkinson's disease

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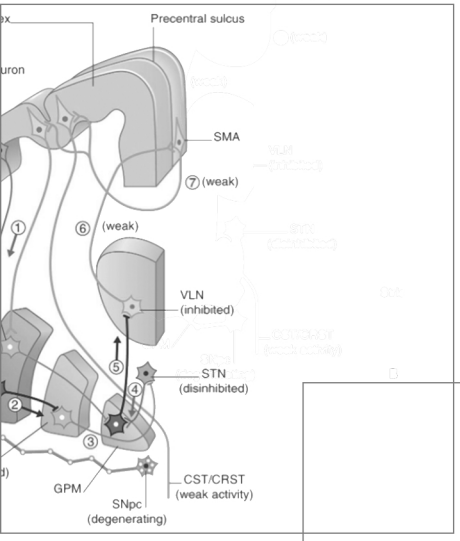
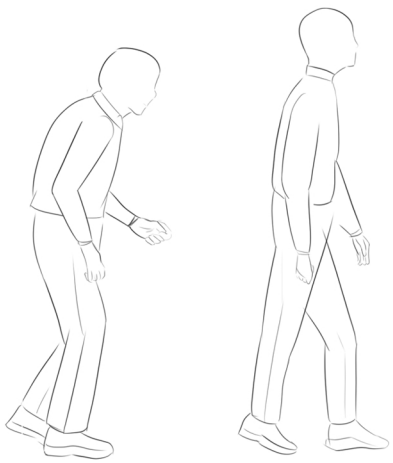
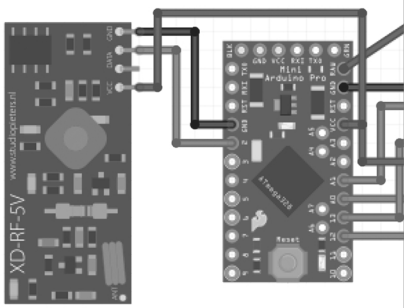



```
void motorControl() {
  if (state != Stop &
>= motorTime) {
    switch (state) {
      case Step0:
        digitalWrite(
        break;
      case Step1:
        digitalWrite(
        break;
      default:
        digitalWrite(
        digitalWrite(
};
motorTime += step
state = (state +
```





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OPPOSING GAIT IMPAIRMENTS DERIVING FROM PARKINSON'S DISEASE

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PREFACE

During my years as a student in the bachelor programme Industrial Design, I developed a special interest in the field of biomedical engineering. The completion of my pre-master in this field demonstrated that design engineering and healthcare prove to be an interesting mix. The performed study pursues that tangent, and this thesis substantiates the executed research.

At very beginning of this paper, I would like to thank those who proved vital to the completion of this research. First of all, a word of thanks to both Jeroen and Marleen for their cooperation. I could not have obtained this level of practical clinical input elsewhere. Additionally, as my faculty based guide, Eric both inspired and allowed me to strive after some unconventional aspirations, and anchored my research when necessary.

Lastly I would like to thank my family and friends for their willingness to submit to my endless monologues concerning this study. In particular my father, who helped me master software I had never encountered before.

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ABSTRACT

Kinesia paradoxa (KP) has been found to relieve gait impairments caused by the progressive neurological disorder Parkinson's disease, in which excessive neuronal cell death ensues causing motor complications. No other common effective method has yet been established to combat motor symptoms effecting gait. Cueing is a relatively novel technique based on KP, which uses a temporal or spatial prompt to improve cardinal symptoms.

A medical scientific protocol has been formulated to test whether this solution pathway is feasible. Using a threefold approach by implementing an anamnesis, a TUG test and a 10 meter walk test, enough input would be generated to draw a conclusion. A LMR dispensation has been filed at the correct METC, to obtain permission to perform this research. After assessment, the dispensation has been denied, thus impeding the patient study.

An Arduino prototype to be employed during testing was designed and assembled using several design phases. Preliminary testing was performed to asses this prototype. Noteworthy differences between regular gait abilities and gait abilities aided by the prototype were found. These test results occasioned the last modifications of the medical device, and the device was deemed appropriate for medical scientific research.

The study results implicate great potential to the medical device. However, feasibility could not be established for no proof of principle study using patients could be performed. To obtain the necessary further research, a positive LMR verdict should be issued by an accredited METC. This process has already been initiated.

LIST OF ABBREVIATIONS

ALS:	Amyotrophic lateral scleroses
CWT:	Comfortable walk test
DBS:	Deep brain stimulation
EMG:	Electromyography
FOG:	Freezing of gait
FWT:	Fast walk test
GABA:	Gamma-Aminobutyric acid
iTUG:	Instrumented timed up and go
KP:	Kinesia Paradoxa
L-dopa:	Levodopa
LMR:	Law medical-scientific research
MAO-B:	Monoamine oxidase B
METC:	Medical ethical testing committee
PD:	Parkinson's disease
QOL:	Quality of life
REM:	Rapid eye movement
SIP:	Stepping in place
SNpc:	Compact part of the substantia nigra
STN:	Subthalamic nucleus
TUG:	Timed up and go
6MWT:	6-minute walk test

GLOSSARY

Ageusia:	Loss of the sense of taste
Aggregate:	Biological phenomenon in which proteins accumulate and clot
Agonist:	Drug with affinity for cellular receptors of a natural substance
Anhedonia:	Inability to experience pleasure
Anosmia:	Lack of the sense of smell
Anticholinergic drug:	Blocking passage of impulses through parasympathetic nerves
Basal ganglia:	Mass of gray matter in central nervous system
Blepharospasm:	Spasm of the orbicular muscle of the eyelid
Bradyphrenia:	Slowness in mental processing
Bradykinesia:	Abnormal slowness of movement
Camptocormia:	Static, forward flexion of the trunk
Corticoretiticular fibres:	Interconnected nuclei located in the brainstem
Corticospinal fibres:	Cells that transfer motor commands from brain to spinal cord
Dopamine:	Neurotransmitter in the central nervous system
Dopaminergic:	Activated or transmitted by dopamine
Dysarthria:	Articulation difficulties caused by muscular control difficulties
Dysautonomia:	Abnormal functioning of the autonomic nervous system
Dysphagia:	Difficulty in swallowing
Dystonia:	Impairment of muscular tonus
Electromyography:	Electrodiagnostic medicine technique
Festination:	Short, accelerating steps paired with postural inaccuracies
Glabellar reflex:	Blinking induced by tapping over the glabella
Hypomimia:	Reduction in facial expressiveness
Inhibition:	Arrest or restraint of a process
Kinesia Paradoxa:	Ability of an akinetic person to exhibit sudden mobility
Micrographia:	Tiny handwriting
Nigrostriatal:	Connection of the substantia nigra to the corpus striatum
Orthostatic hypotension:	Abnormal decrease in blood pressure when standing up
Paresthesias:	Prickly, tingling sensation
Parkinson’s disease:	Neurodegenerative disorder of the basal ganglia
Proteasome:	Cytoplasmic organelle responsible for degrading proteins
Quality of life:	Overall assessment of a person’s wellbeing
Scoliosis:	Side-to-side curvature of the spine
Seborrhea:	Excessive discharge from the sebaceous glands
Sialorrhoea:	Hypersalivation
Striatal deformities:	Abnormal postures in hand and foot
Striatum:	Central nervous system area
Substantia nigra:	Layer of large pigmented nerve cells in the midbrain
Subthalamic nucleus:	Basal ganglia nucleus which is a satellite of the globus pallidus
Ubiquitin:	Protein associated with intracellular protein breakdown

CHAPTER 1: INTRODUCTION

Parkinson's disease (PD) is the second most widespread progressive neurological ailment. Following Alzheimer's disease in patient scope, PD affects over 7.5 million people worldwide and 70 000 of these patients are currently living in the Netherlands. Given the fact that the risk of attaining PD increases with age, the number of patients rises progressively as the median age of the world increases steadily [1]. Despite the enormous amount of effort and research that is executed in the field of PD, there is no cure yet available to treat the disease [2].

The clinical image of PD is different for each patient, yet consists of the same building blocks in the cognitive, sensory, psychological and motor error range [3]. Most distinctive is the loss of control over basic motor skills. This results in several characteristic symptoms, such as resting tremor, hypokinesia (decreased bodily movement) and loss of balance [4]. PD imposes a heavy burden on quality of life (QOL). Motor symptoms that contribute most to a decline in QOL are medication related impediments and gait impairments [5]. Furthermore, gait deficiencies are widely associated with loss of independence and an increased chance of falls [6].

Although PD is a progressive disorder, a partial temporary recovery from gait impairment is possible. Similar to clinical pictures like dysarthria and autism, PD patients are susceptible to the phenomenon Kinesia paradoxa (KP). Patients with severe walking impairments can exhibit sudden increases in mobility when stimulated suitably [7]. Research has shown that external sensory cues can help the patient retain a regular gait [8].

1.1 RESEARCH PURPOSE

Within the framework of the project "Ontwerpen voor een specifieke doelgroep" at the University of Twente, preliminary exploration occurred in order to develop a rehabilitation device. This research paper is dedicated two ways. First and foremost, the goal is to verify the potential of the designed cueing technique. Additionally, the rough concept previously produced will be enhanced and explored. The design-oriented partition of this study will serve to support the Proof of Principle research goal. In order to achieve these ends this paper centres around the following fundamental research question:

Is it feasible to oppose gait impairments deriving from Parkinson's disease effectively by using a tactile-based cueing device?

In order to execute the appropriate research correctly and to ensure well-organised documentation, the following sub questions have been formulated:

- *Which methods are conceivable to combat gait impairments caused by Parkinson's disease?*
- *How can the effectiveness of the product be measured?*
- *In what way should the current prototype be improved?*
- *What are the implications of the use test on the feasibility of the potential of the cueing device?*

1.2 DOCUMENT GUIDE

Following this introduction, **Part I: theory** will study the relevant aspects of PD and its implications on gait. **Chapter 2** will be essential in the process of gaining insight into the clinical picture of PD and the associated walking deficiencies. Furthermore, this chapter will attend the solution pathways to be explored in order to result in the intended operative method. Subsequently, **chapter 3** will consider the way in which the feasibility of the product will be verified. Using this

knowledge, a comprehensive experiment will be designed in order to establish or repute the potential of the product.

Part II: design will encompass the design-oriented division of this research. In **Chapter 4** the current rough concept will be refined to ensure the incorporation of new knowledge and to ascertain it fits the designed use test optimally.

The final stage, **Part III: results and implications**, was intended to cover the processing and interpretation of the test results. However, it was found that obtaining consent to perform medical scientific research was a more complex process than could be reasonably expected, and an unforeseen glitch was encountered. The research could not be performed and therefore no results are available to discuss in part III.

Nonetheless, **Chapter 5** will contain the conclusion to be drawn from the remaining research, and **Chapter 6** will touch upon the recommendations that can be made.

CHAPTER 2: THE IMPLICATIONS OF PARKINSON'S DISEASE ON GAIT

This chapter pertains the relevant aspects and implications of Parkinson's disease and its repercussion on gait functioning. The core research objective here is to answer the following question:

Which methods are available to combat gait impairments caused by Parkinson's disease?

In order to create a clear overall picture, this research question has been split into the following four sub questions.

- *What is Parkinson's disease?*
- *What are the consequences of Parkinson's disease on gait?*
- *Which solution pathways are viable to reduce gait impairments?*
- *What is the intended operative method for the product?*

2.1 PARKINSON'S DISEASE

In 1817 the English doctor James Parkinson published his would-be most famous work: *An essay on the Shaking Palsy*. With remarkable accurateness, he defined the symptoms of a yet largely undocumented disease. The description of the disease that would bear his name is poignant: "*...the unhappy sufferer has considered it as an evil, from the domination of which he had no prospect of escape. [9]"* To this day, the disease intrigues doctors and scientists alike for no cure and no definite cause has been found as of yet.

The clinical diagnosis of PD typically depends on the characteristic impairment of motor functions. In addition, the pathology of PD results also in a great number of non-motor symptoms [10]. The extensive list of symptoms is depicted in Table 1.

Table 1: *Parkinson's disease symptoms [11].*

Motor symptoms	Non-motor symptoms
Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, Bradyphrenia, tip-of-the-tongue (word finding) phenomenon
Hypomimia, dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioral and psychiatric problems
Decreased arm swing, shuffling gait, festination, difficulty arising from chair and turning in bed, freezing of gait	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
Micographia, difficulties cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhea), weight loss
Glabellar reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behavior disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

As to the exact underlying pathology of this disease, uncertainties remain. What is known is that PD is a progressive neurodegenerative disease. This conveys that there is a gradual disintegration of dopamine producing neurons in specific parts of the brain. Since dopamine contributes to regulation of movement, this results in the clinical image of PD. Additionally, PD has a profound effect on certain nondopaminergic nuclei. This pathological feature correlates mostly with the non-motor PD symptoms and will not be

discussed in detail in this research paper.

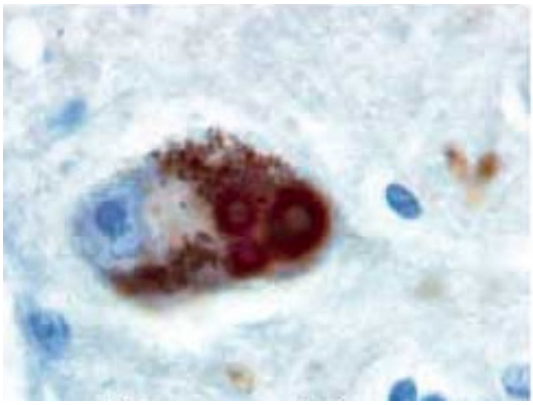

Figure 1: *PD, Lewy bodies labelled for alpha-synuclein (fine granular brown label in this panel represent neuromelanin) (substantial nigra). [12]*

The neuropathological characterization of PD is defined by the presence of Lewy-bodies and Lewy-neurites in the dopamine producing neurons. Using this reference point, an enormous amount of research has been devoted to the exact implications of the presence of Lewy-body pathology. Biochemical and immunohistochemical research has shown that these Lewy-bodies consist predominantly of protein clumps of which the main component is alpha-synuclein [13]. Figure 1 depicts such a distinctive Lewy body in which the protein alpha-synuclein is stained.

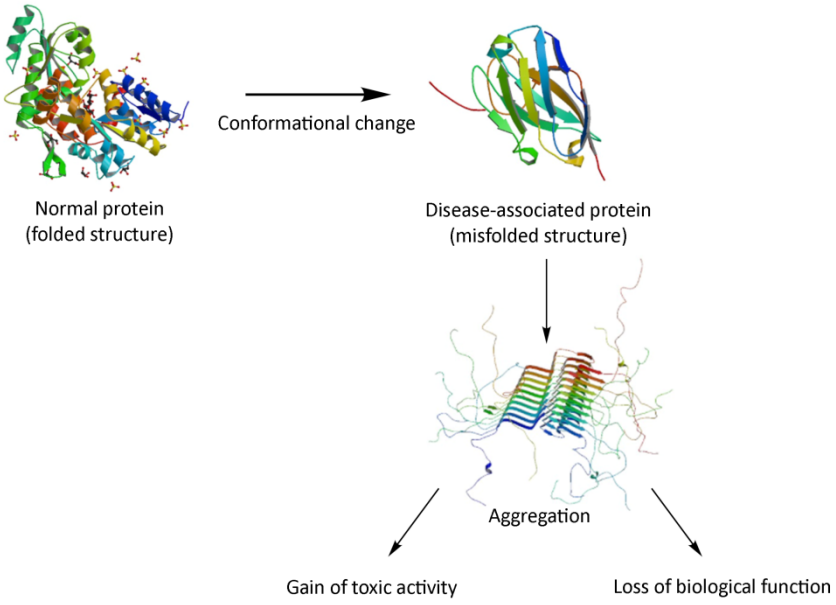

Figure 2: *Schematic view of the results of conformational changes of alpha-synuclein*

Toxic buildup of misfolded proteins transpires in numerous neurodegenerative diseases, such as Alzheimer's disease, Amyotrophic Lateral Scleroses (ALS) and Huntington's disease. The conformation of a protein causes its unique secondary structure which is essential for regular functioning. When preventive measures against protein misfolding, such as ubiquitination and associated proteasome activity, fail to dissociate a misfolded protein the consequences may be severe. An aggregate consisting of amyloid fibrils is formed which leads to a gain of toxic activity and/or a loss of biological function. In

Parkinson's disease, the soluble alpha-synuclein misfolds into an insoluble aggregate and accumulates in the dopamine producing neurons in the brain [14]. A schematic view of the misfolding of alpha-synuclein is provided in Figure 2.

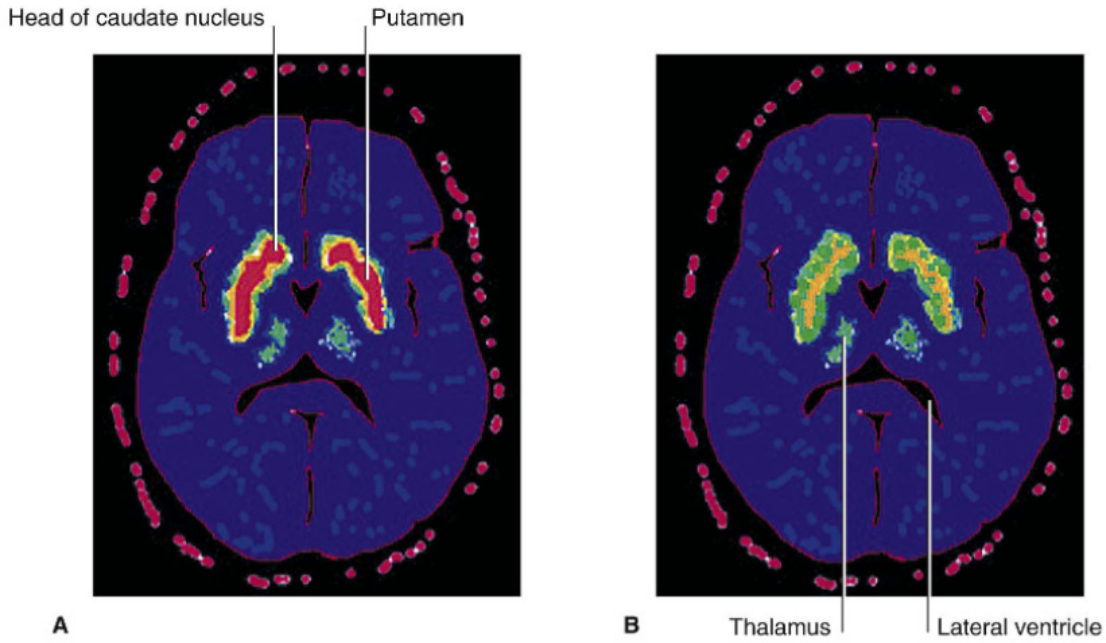

Figure 3: *Diagram showing typical results of brain scans following intravenous injection of [18F] fluorodopa. Fluordopa binds with dopamine receptors in the striatum. Intensity of uptake is indicated as red (greatest), yellow, green, blue (least). (A) Control; (B) Parkinson's disease [15].*

These nigrostriatal neurons degenerate, which results in a strong decrease of dopamine content in the striatum. Most commonly approximately 60% of the neurons has been lost already when the initial recognizable symptoms appear. This suspension of symptoms is accounted for by the fact that the responsible systems in the brain are able to compensate the loss of neurons at first [16]. When the dopamine production truly wavers, the characteristic PD symptoms are expressed. Figure 3 shows the difference in dopamine concentration in the brain of a patient with Parkinson's disease and the brain of a control group.

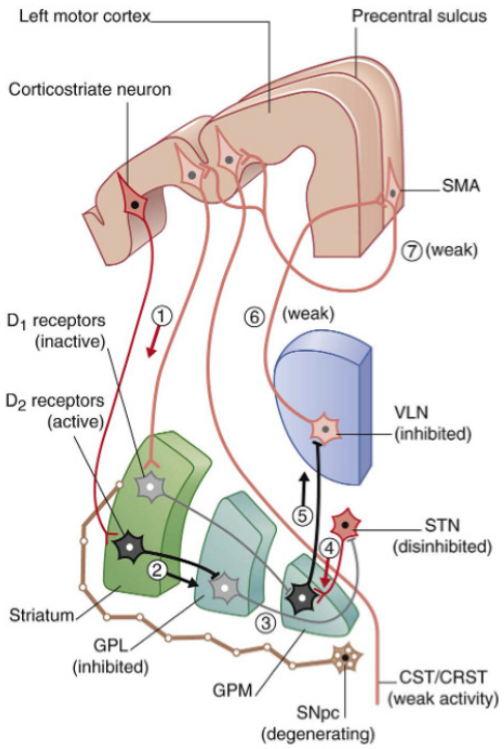

Figure 4: *Consequences of degeneration of the pathway from the compact part of the substantia nigra (SNpc) to the striatum (S) in Parkinson's disease illustrated in a coronal section through the motor loop [15]. Note the weakened output activity.*

The neurons in the substantia nigra are part of the dopaminergic nigrostrial pathways, a complex communication route in the brain. These pathways are essential in the functioning of the direct pathway in the motor loop that controls learned movement. They project from the substantia nigra to the striatum and are responsible for feeding neurons forward to the motor cortex. As a result of PD, the direct motor pathway is disabled and the indirect motor pathway in activated by default. This leads to disinhibition of the subthalamic nucleus. Furthermore, input from the supplementary motor area to the corticospinal and corticoreticular fibers deteriorates increasingly which has severe negative consequences on ignition and execution of movements. In short, the damage to the motor pathways in the brain reduces the ability to initiate movement in the direct pathway, and lowers the ability to prevent an excessive reduction in voluntary movement. This results in the bradykinesia and the loss of movement associated with Parkinson's disease [15]. This development is illustrated in Figure 4.

2.2 CONSEQUENCES OF PARKINSON'S DISEASE ON GAIT

Parkinson's disease is known to interfere with several aspects of quality of life. Physical and social functioning appear to be the most affected areas [17]. Mobility and gait limitations are major problems for PD patients. These symptoms are not limited to physical discomfort, but also impact social functioning significantly. Figure 5 depicts the social and physical implications of walking deficiencies associated with PD. Gait disorders have, next to depression and dopaminergic medication related complications, the greatest influence on perceived quality of life [18]. Therefore, the improvement of these features can bring about enormous enhancement in quality of life for Parkinson's patients [19].

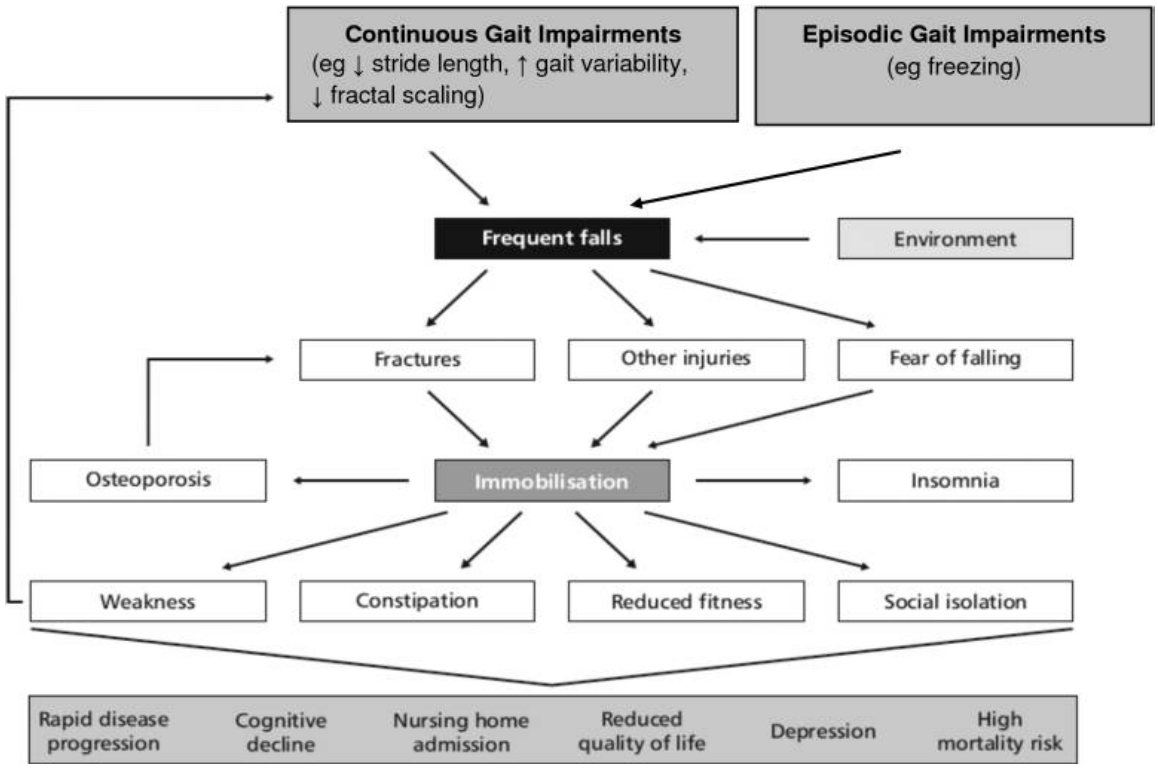

Figure 5: *Clinical impact of instability and falls in patients with PD. Note the vicious cycle that arises as a result of gait instability and impairment [20].*

Gait disturbances in PD, also called Parkinsonian gait, can be divided into two categories. Symptoms that are catalogued in the category continuous gait impairments appear to be consistent modifications in the walking pattern. The category episodic gait impairments encompasses walking disorders that occur irregularly and sporadically. These symptoms occur in an as of yet inexplicable manner [21]. Symptoms of both categories contribute to gait impairments and increases risks of fall associated with PD and are depicted in Table 2.

Table 2: *Parkinson's disease symptoms that contribute to gait impairments and according categorization [22].*

Symptom	Category	Description
Slowed ambulation/hypokinesia	Continuous	Predominantly a manifestation of bradykinesia
Arm swing alterations	Continuous	Decreased/absent arm swing
Increased double limb support	Continuous	Increased amount of time spent with both feet on the ground
Postural instability	Continuous	Loss of balance
Decrease stride length	Continuous	Inability to generate appropriate stride length
Festinant gait	Episodic	Shuffling, rapidly accelerating steps
Freezing of gait (FOG)	Episodic	Episodes of inability to step
Start hesitation	Episodic	Difficulty initiating walking movements. Element of FOG

2.3 SOLUTION PATHWAYS FOR PARKINSON'S ASSOCIATED GAIT IMPAIRMENTS

As a cure for Parkinson's disease is not yet discovered, patients rely on symptom control to optimize physical and social functioning. Noteworthy is that certain mobility difficulties are rather resistant to medical treatment. These gait impairments therefore may warrant an innovative multidisciplinary restoration method [18]. In this section viable and feasible solution pathways to combat gait impairments are listed and discussed.

Medication
Pharmacological therapy is the most conventional means to alleviate PD symptoms. Several drug categories are in use, for example MAO-B inhibitors, dopaminergic agonists (DA) and anticholinergic drugs. However, none of these drugs obtain the same effectiveness as Levodopa (L-dopa) [23]. Levodopa is most often paired with a dopa decarboxylase (DDC) inhibitor and is metabolized to dopamine in the brain. This reaction is shown in Figure 6 and replenishes striatal dopamine in the substantia nigra. The central motor features of PD are repressed by this treatment.

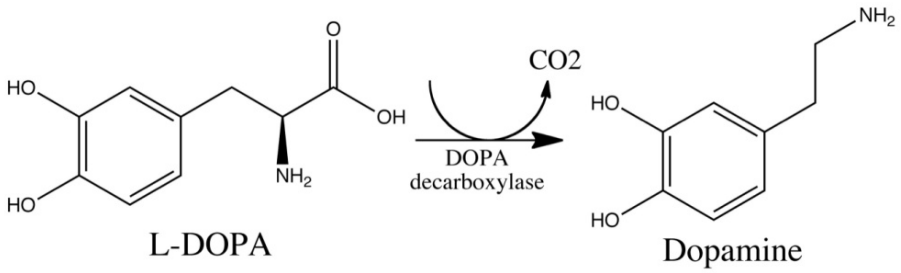

Figure 6: *Chemical reaction of the synthesis of dopamine from L-dopa [24].*

The discovery of L-dopa was a dramatic breakthrough in neuroscience. Patient that were perpetually frozen could suddenly walk again. In his book *Awakenings,* which was published in 1973, Oliver Sacks describes this effect as follows: "*The patient on L-dopa enjoys a perfection of being, an ease of movement and feeling and thought, a harmony of*

relation within and without." Shortly thereafter however, the drawback of this medicinal wonder became clear: "*Happy state –his world– starts to crack, slip, break down, and crumble; he lapses from his happy state and moves toward perversion and decay [25]."* To this day, clinicians often opt to postpone the use of L-dopa for as long as possible. A delicate equilibrium exists, which balances a risk of under treatment of PD and the notorious side-effects of L-dopa. Following an initial stage of dramatic benefit, dreaded side effects become apparent [26].

Table 3: *Long term complications of levodopa treatment [27] [28].*

Drug related side-effects	Dopa-resistant non-motor symptoms	Dopa-resistant motor symptoms
Motor fluctuations (On/Off effect)	Autonomic dysfunction	Postural abnormalities
Dyskinesias and Dystonias	Mood impairment	Freezing episodes
Psychosis	Cognitive impairment	Speech impairments
"On" state FOG		

Table 3 illustrates the long term complications of L-dopa. The described motor complication can be very disabling and are difficult to treat. Note that several of these limitations impact gait, namely postural abnormalities, freezing episodes, dystonia and dyskinesia. Existing management of motor complications is deemed less than satisfactory and therefore L-dopa is not ideal to target gait impairments adequately.

Deep brain stimulation

An emergent neurosurgical technique to aid restoration of lost brain function is the use of electrical stimulation. A device that targets the subthalamic nucleus (STN) in the brain through deep brain stimulation (DBS) has the potential counteract the symptoms associated with PD [29]. The proposed mechanism of this procedure is the paralysis of the excitatory message sent from the STN to the GABAergic reticular of the medial pallidal segment (GPM). The inhibitory supply to the locomotor center that is characteristic of PD is blocked, which causes the disinhibition of the locomotor center and thereby relieves the symptoms associated with PD [15]. Figure 7 illustrates motor loop functioning with and without the presence of a STN-DBS.

However, similar to L-dopa, deep brain stimulation is not without complications. The placement surgery on its own is non ablative and minimally invasive, yet research has shown that irreversible and unadaptable complications and side effects may arise. Brain surgery in itself is associated with (a minimal risk of) complications like paralysis and hematoma. Furthermore, STN-DBS placement can bring about hardware problems, such as lead fracture, dislocation an infection. Moreover, the chronic stimulation of the brain itself can cause side undesired effects [30]. Lastly, STN-DBS stimulation is associated with mood changes [31] and behavioural complications [32]. A renowned case in which this problematic feature is observed was brought to light in 2004 by Leentjens et al. The published article describes the ethical dilemmas associated with a case of a PD patient that benefited greatly from a STN-DBS. His improvement, however, was accompanied by a significant drawback. The patient was in a stimulation-related manic state and did not respond to stabilizing medication treatment. He arrived at a point where his conduct was no longer socially acceptable: he took on a married mistress and bought a second house for her. In addition, he bought multiple cars, was implicated in several traffic incidents and lost his driver's license. With no therapeutic margin between his bedridden

parkinsonian state and his maniac symptom-free state, an ethical dilemma arose. Admit a mentally sane man to a nursing home because of his severe invalidity, or admit the patient to chronic psychiatric ward because of his PD symptom-free manic state? In the end, the patient chose the second option when not being stimulated [33].

Abovementioned case and complications illustrate the fact that while STN-DBS has great potential for enabling PD patients, an undesirable trade-off may be inevitable.

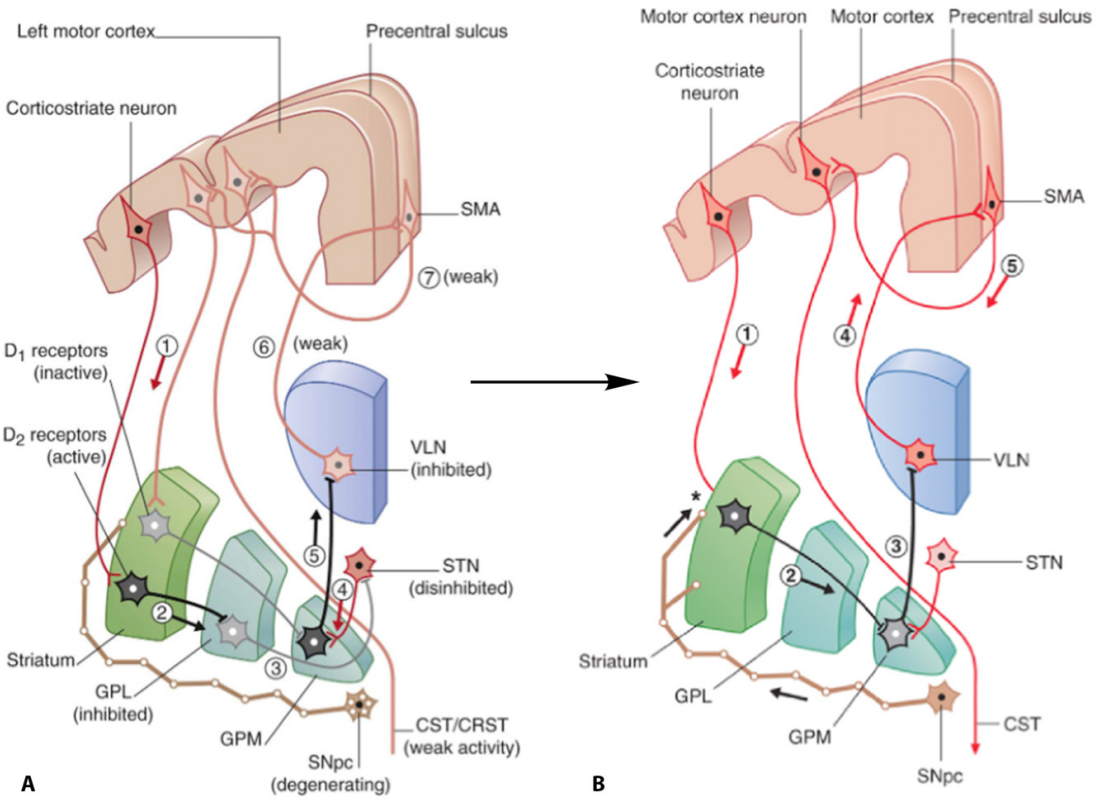

Figure 7: *Coronal section through the motor loop. (A) motor loop functioning in PD patients (B) ideal functioning brought on by an STN-DBS. Note the increase of output activity [15].*

Exercise

Patients with Parkinson's disease are often prone to a sedentary lifestyle [34]. As mentioned in paragraph *2.2 Consequences of Parkinson's disease on gait*, immobilization may evolve into a vicious circle which ends in rapid disease progression, cognitive decline, nursing home admission, reduced quality of life, depression and even a high mortality risk. Research has shown that frequent, multimodal exercise [35] has a positive effect on both motor and non-motor PD symptoms [36]. The symptomatic and supposed neuroprotective benefits from exercise confirm its use as an additional measure to combat gait impairments. Evidence suggests that workouts can improve stride length, quality of life and motor response to levodopa. Therefore exercise is a valuable asset to any treatment plan for PD [23].

Cueing

Cueing is another relatively novel technique to improve gait in PD patients, and is based on the phenomenon kinesia paradoxa (KP). Kinesia paradoxa is an abrupt and temporary loss of akinesia or other walking inhibitions, both continuous and episodic [37]. The most common hypothesis for this occurrence postulates that outer sensory prompts can be vital in provoking a substantial decrease in gait impairments. An alternative

hypothesis states that the expectation of a prompt rather than the actual prompt itself is responsible for the emergence of paradoxical kinesia [38]. For this research, the underlying theorem is not quite as relevant as the consequences of KP. Whether the actual cue elicits the desired response or the anticipation is responsible for the improvement of gait, fact is that when a cue is offered to a PD patient walking patterns can improve.

Similar to the nature of the prompt, the actual process by which a cue improves cardinal symptoms of Parkinson's disease remains unclear. The generally recognised proposition states that the neuronal process which underpins goal-directed movements differs fundamentally from the neuronal process that controls automatic movements. It is postulated that a cue may provide the means to entirely bypass the malfunctioning basal ganglia circuitry [39]. A noteworthy consequence of this proposed mechanism is the fact that constant vigilance might be required in order to prevent the PD patient from reverting to habitual regulation mechanisms [40].

While severe gait deficits such as FOG are often resistant or worsened by pharmacological [41] and surgical intervention [42], research shows that temporal and spatial cueing techniques could improve gait pathology significantly [43].

The future of PD treatment

Lastly it is noteworthy that stem cell grafts, gene therapy and other innovative medical progressions may serve to treat or even cure PD. These approaches are researched intensively and hopefully will one day empower PD patients [44]. However, as these experimental treatments are still awaited, abovementioned existing techniques should be applied to relieve symptoms.

2.4 INTENDED OPERATIVE METHOD

CHAPTER 3: MEASURING THE EFFECTIVENESS OF THE DEVICE

The purpose this chapter serves, is to formulate the way in which the operation method of the designed device will be put to the test. This chapter is essential in formulating the scope of this research. Hence, it is important to keep in mind the proof principle framework of this project. The corresponding research question is defined as follows:

How can de effectiveness of the device be measured?

To underpin the answer to this question carefully with the appropriate research, the following sub questions have been formulated:
- *What gait analysis methods can put the device to the test?*
- *What are relevant indicators in testing the device?*
- *What is the intended testing protocol?*
- *How can permission to perform this research be obtained?*

3.1 GAIT ANALYSIS METHODS

When endeavouring to verify the potential of this cueing device, it is important to ensure that the assessment of the efficacy of the intervention is carried out correctly. Since the typical gait disorders of PD include numerous different factors, and each contributes to an unpredictable extent to impairment, gait-analysis technology is a notoriously complex field. As numerous options to qualify gait are available, this section will pertain the most relevant and customary options.

Laboratory-based gait analysis
This testing method is widely accepted to be the ‘gold standard’ in gait analysis, for it measures position accurately and provided well-quantified and accurate results over brief distances. In general, the laboratory-based gait test is performed in a standard gait laboratory by using specialized technology. A combination of optical motion measurement system and a force platform is linked to a computer, and provides a way to gather data on the studies subjects gait. This technique is usually supported by an electromyography (EMG) system to record muscle activity during gait. Therefore, not only the kinematics and kinetics of gait are examined, the muscle activity is also detected and analysed.

However, this method has several disadvantages that disqualify it for the use in this research. It is known that this method is unsuitable for measuring acceleration and evaluating gait during varying circumstances. In addition, few researchers have validated objective symptoms measurements against self-perception data. Furthermore, only a limited number of consecutive strides can be measured, the equipment is expensive and cumbersome and the set-up time is extensive [47].

Ambulatory gait analysis
A more recently developed method is the ambulatory gait analysis. Wearable inertial sensors such as accelerometers and gyroscopes are attached to relevant parts of the body. These devices transmit recorded data to a computer which in turn processes the received signals. The equipment is portable and less bothersome than laboratory-based gear. Gait parameters are quantified continuously, acceleration is appropriately measured and brief events are recorded suitably. Furthermore, the equipment can be carried for long periods and distances, which ensures that not only laboratory conditions are taken into account [48].

Conversely, the system appears to be poor at determining position and validation is required to determine real-world performance. Another disadvantage of this equipment is that it should be adjusted to the walking style of each individual user [47].

SIP task
The stepping in place (SIP) task consists of a PD patient alternating steps on two force plates. The SIP paradigm provides a technique to measure several gait variables, including step coefficient of variation, rhythmicity and asymmetry. Furthermore, it is remarkably accurate in the assessment and identification of FOG [49]. While renowned for its accuracy in gait analysis, it does not simulate normal situations. As seen previously in section 2.3, normal attentiveness to walking patterns may be essential to appropriate testing and therefore the importance of imitating an ordinary environment cannot be understated [39].

TUG test
The timed up and go (TUG) test is a broadly used simple clinical model to appraise gait and balance. A timed analysis of a series of activities is performed. The TUG sequences several mobility skills: the patient is most commonly asked to get up from a chair, walk 3 meters, turn 180 degrees, walk back to the chair and sit down. Several variations on this configuration have been used in order to support a specific research completely [50] [51]. The main advantage of this test is that it resembles a normal patient situation closely. Moreover, it can be altered to optimally fit the research perspective. By simulating narrow pathways, symptoms that are notoriously difficult to provoke in test situations can be triggered. The test is relatively easy, and required components can be incorporated, such as the identification of freezing moments.

The main limitation of TUG is the fact that it cannot identify different mobility deficits and focuses only on gait as a whole. In order to assess and qualify individual gait symptoms instrumented TUG (iTUG) has been developed. In addition to the TUG test, iTUG uses gyroscopes to analyse gait patterns throughout the process [52].

Short-distance walking speed test
Another test that has proven to be reliable and responsive to gait changes in persons with PD is the short-distance walking speed test. Several versions of this test exist, such as the 10-meter walk test, the 6-minute walk test (6MWT). The 10-meter walk test consists of two variations: the comfortable walk test (CWT) and the fast walk test (FWT). The patient is subjected to either or two tests in order to determine functional mobility, gait and vestibular function. The test consists of a trajectory between two markings, and the time spend between passing the first marker to passing the second is recorded. CWT and TWT test can either be used in combination or separately and are known to distinguish changes in gait function impairments accurately [53].

3.2 RELEVANT INDICATORS

Carefully controlled and documented conditions are imperative when executing a patient-based test. This section concerns the various relevant indicators pertaining the assessment of gait disorders.

Homogenous patient group
A homogenous patient group is often essential to establish reliable research results. As PD is associated with a wide array of symptoms and severity, clinical evaluation of the patient group as a whole is vital. Either patients should be included or excluded based on clinical image, or participant characteristics should be carefully registered and considered.

The study population is comprised of non-emergent PD patients over 18 years old, that will be recruited from the neurology clinic at the MST. Generally, approximately one eligible patient is treated every week. To be suitable to participate in this study, a subject must meet all the following criteria:

- Exhibit gait impairments caused by PD
- Age ≥18 years old
- Visit the neurology clinic at MST as part of standard clinical care for Parkinson's patients

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Unable to provide written informed consent
- Exhibits advanced non-PD related gait impairments or musculoskeletal deficiencies
- Suffers from interfering neurological issues, such as significant cognitive deterioration which causes the patient to be unable to understand the research purpose and accompanying instructions

The subject-related factors depicted in Table 4 will be registered during this research, for they may impact the extent to which the device could influence walking impairments.

Table 1: *Relevant participant characteristics*

Factor	Notes
Age	(years)
Elapsed time since diagnosis	(years)
Score on Hoehn and Yahr scale	(1-5) System commonly used to describe disease progression in PD.
Medication state	(ON/OFF) Gait impairments can either be worsened or relieved by dopaminergic treatment and therefore it is necessary to register whether the patient is either in an OFF medication state (long-acting dopaminergic medications were stopped ≥24 h prior, and short-acting medications were stopped ≥12 h prior to testing) or an ON medication state (regular administration of drugs).
FOG questionnaire	(multiple choice) Questionnaire to asses FOG severity and gait difficulties in general. Significant because FOG's unpredictable presentation, sensitivity to medication, cues and heightened attention make it difficult to trigger FOG during research [54].

Deliberate concentration

As mentioned in section 2.3, increased attention to gait patterns itself may bypass malfunction in the basal ganglia circuitry wholly, and therefore alleviate gait impairments. It is common for patients to show remarkable improvements in testing situations as opposed to habitual settings. The intended testing method should take this increased vigilance factor into account, and try to regulate this influence.

Placebo effect

Numerous medical conditions are subject to placebo responses. This effect is encountered exceptionally often in Parkinson's disease and related treatments. Research has suggested a direct link between the placebo effect and reward mechanism. Dopamine, which plays a vital role

in instigating PD, is also the major neurotransmitter in the reward circuitry. Substantial amounts of dopamine are released in specific parts of the striatum when the placebo effect is observed in PD-related subjects. This sudden dopamine production ameliorates PD symptoms significantly and can be encountered in any type of PD treatment. Therefore, PD treatment can always be subject to the placebo effect and it is a relevant factor in PD-related research [55]. As this research is a small-scale pilot study, the placebo effect does not fit its scope. However, its inclusion is an important recommendation if further research is conducted.

3.3 INTENDED TESTING METHOD

As this research follows the proof of principle methodology, a small-scale testing process has been designed. The testing itself will consist of minimally burdensome standardized tests, and the acquired information will be processed fully anonymously in order to avoid breaches of patient integrity and privacy. The official patient briefing can be found in **appendix 1** and the accompanying research protocol is included in **appendix 2.**

The testing method can be divided into three phases. First a fundamental anamnesis will take place, followed by a TUG test and a short-distance walking speed test. The way these phases contribute to allotment of research value is described in the following paragraph.

Anamnesis
This test section pertains the medical history of the subject. The aim is to obtain the relevant participant characteristics, as mentioned in section 3.2. Controversy, PD symptoms often contrast with clinical signs. This anamnesis is essential in establishing perceived symptoms, while the clinical signs will be ascertained by the following research steps. The implemented anamnesis can be found in **appendix 1** and includes not only questions to ascertain clinical signs but also on perceived indicators.

TUG test
The TUG test provides a reliable and minimally invasive method of classifying the gait capabilities of a subject and offers a perfect fit for this research [56]. The TUG test consist of a simple, minimally taxing series of activities. Furthermore, the included 180 degree turn notoriously provokes FOG episodes.

Figure 1: *TUG illustration*

The subject is asked to get up from a chair, walk 3 meters, turn 180 degrees, walk back to the chair and sit down, as illustrated in Figure 8. Following a rehearsal test, the actual test will be carried out. The starting signal is accompanied by starting a stopwatch, and the elapsed time

before the patient returns to the chair and in immobile is measured. The test is carried out at least two times, of which an average value will be noted and used for further analysis. As this research aims to compare regular PD-related gait impairments and gait impairments influenced by the cueing device, the definite test will be performed three times.

- First off, to familiarize the patient with the testing situation and to measure habitual gait
- Secondly to establish gait when the device is attached, but not activated. The action sequence is performed twice without an activated device
- And lastly in order to ascertain the effect of the device on gait, the action sequence is performed twice with an activated device

Short-distance walking speed test

Lastly, the 10-meter walk test will be performed. In this short-distance walking speed test, the subject walks 10 meters at a comfortable pace, as illustrated in Figure 2. The time spend between passing a 2-meter and an 8-meter marker is measured.

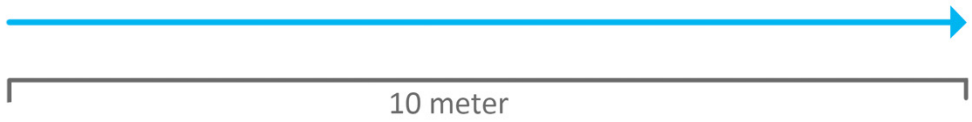

Figure 2: *10-meter walk test illustration*

In this test, value will be allotted not only based on interval measurements, but also on number of freezing episodes and step count. Video footage of the test will be acquired and number of steps will and number of freezing episodes will be evaluated by two researchers separately. This test will be performed six times, and the cycle sequence will be changed throughout to avoid operant conditioning.

- First off, the trajectory will be traversed thrice to establish device effectiveness in normal circumstances, using the same tasks as during the TUG method but in a different order
- Secondly, the trajectory will be traversed thrice again using these tasks to establish the effect of the device when deliberate concentration in targeted and minimalized by adding a manual component. The subject is asked to balance a cup filled with water while walking the allotted distance

Perceived effect

When the three different phases have been completed, the patient will be asked to rate the general experienced effect, using a provided scale. This scale can be found in **appendix 2.**

3.4 RESEARCH PERFORMANCE PERMISSION

To perform accredited research, the protocol of every medical scientific study involving human beings must be assessed on ethical and juridical aspects by a Medical Ethics Testing Committee (METC). Medical scientific studies encompass studies in the field of sickness and health, that occur by systematically gathering and examining data. Furthermore, the study strives for adding to the medical body of knowledge that also embodies populations outside the direct research population. As this research fits the characteristics of a medical scientific study, the research cannot be performed if the METC does not grant permission.

The METC categorizes scientific medical studies into two partitions. Either the study is subject to the Law Medical-scientific Research (LMR) or the study is not. A study is per definition

specialized as LMR if the study is part of a scientific medical research, and actions or rules of conduct are imposed to patients. Furthermore, all medication research protocols are subject to LMR. However, practice reveals that cases of doubt are abundant, and that a rather large grey area exists in which LMR is not readily imposed or discarded.

Receiving permission to perform a LMR study is a tedious, time consuming and costly process. In contrast, non-LMR studies are relatively readily assessed by the METC.

This medical-scientific study is a small-scale, non-invasive research based on the proof of principle method. The extend of the burden on the patient is minimal, for the performed actions will not exceed habitual movements. Moreover, the prototype will be designed to ensure optimal safety and the risks associated with the product will be minimized. Both doctors of the neurology department involved in this research deemed in feasible that this study would be declared not subject to the LMR. Therefore, the METC has been petitioned to asses this research as a non-LMR study.

A non-LMR assessment would ensure that the medical scientific study fits the scope of this research. A LMR study would impose such an increase in invested time that it is not feasible to be performed within the constraints of this research project.

Assessment procedure

Unfortunately, the METC deemed the study to subject to the LMR. This verdict is based on the fact that a scientific research question was formulated, and the nature of the study. Instead of categorizing this research as a pilot study, the study was considered to be an intervention study with a medical device. Furthermore, the fact that the prototype was no quipped with a CE-marking was a hindrance.

Consequently, the study could not legally be performed without attaining a positive complete LMR-assessment and a positive inspection report issued by a medical technical service.

Passing this strict examination is a time consuming and extensive procedure which does not fit the scope of this research. Therefore, no patient testing can be performed within the constraints of this project.

CHAPTER 4: DESIGN OF THE MEDICAL DEVICE

This chapter encompasses the re-design of the prototype that will be employed during testing. The main question that will be answered in this section is formulated as follows:

In what way should the current prototype be improved?

To answer this question, a basic engineering design process will be followed to analyse the current prototype and define accompanying problems. Thereafter, specify the appropriate requirements and define a solution. The following research questions will be leading in this process.

- *What is the status of the rough concept?*
- *Which limitations of the rough concept hinder application?*
- *How will the desired modifications be administered to develop a suitable concept?*
- *Will the new concept perform suitably in a preliminary test?*
- *What adjustments are necessary to realize a refined concept?*

4.1 ROUGH CONCEPT

4.2 LIMITATIONS

4.3 DEVELOPED CONCEPT

In first phase of the engineering design process, the choosing of an appropriate software-hardware combination is essential. When the design requirements are considered, a suitable platform can be selected and the necessary functionality can be implemented.

For this project, the Arduino system of hardware and software fits the purpose perfectly. As an open-source system with accessible and relatively inexpensive elements, this appears to be an attainable target.

Now the platform is established, the design requirements can be transformed into functionality.

Prototype solution stage I

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Prototype solution stage II

Prototype solution stage III

4.4 PRELIMINARY TEST

Using the developed prototype, a preliminary test was designed. The aim of this study was to examine and evaluate the prototype setup. The test results will be assessed to determine whether the device has any effect on impaired gait caused by PD for this patient, and whether adjustments to the design would be beneficial to prototype performance.

Method

This study pertains one participant with PD induced gait impairments and severe freezing symptoms. As the study aims primarily to fit design purposes one participant should provide enough feedback to adequately meet the analysis demands. The subject was, during testing, in an OFF-medication state to negate the effect of dopaminergic drugs on walking abilities.

The measure featured to evaluate gait was a standardized TUG-test, which was performed thrice.

- Once to ascertain habitual gait
    - The patient performed the TUG test regularly
- Again, to determine whether wearing the device itself had any effect on gait performance
    - The patient performed the TUG test while sporting the inactivated prototype
- Lastly to establish the effect of the activated device on gait impairments
    - The patient performed the TUG test again, this time supported by the activated device

The primary study parameter is the time it takes for the patient to complete the prescribed TUG test. The results of the repeated test will be compared to see if improvements can be ascribed to situations.

Two secondary study parameters are considered, the number of freezing episodes the subject experiences, and secondly the number of steps the subject needs to traverse the trajectory. Likewise, value will be allotted to these parameters by comparing the repeated tests in which the situation was altered.

After the initial tests have been performed calibration of the number of steps will take place, and the TUG test will be performed once more to establish effectiveness.

Results

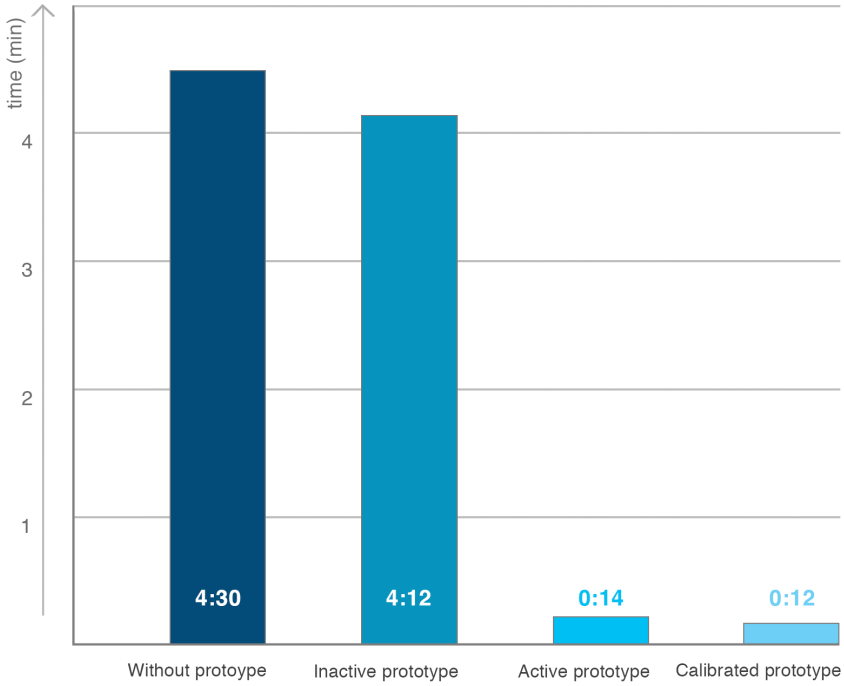

Figure 10: *Elapsed time in minutes, plotted against the separate situations*

The elapsed testing time differs greatly when comparing testing situations, as depicted in Figure 10. The results can accordingly be categorized into two distinct categories.

The first category encompasses both tests that occurred without an active prototype. These variations both took over 4 minutes to complete. Whereas the remaining tests using an active prototype show a noteworthy reduction in elapsed time, and took respectively only 0:12 and 0:14 minutes. These test results are considered in the second category, where great improvement of gait impairments was observed.

The two categories show no bilateral exceptional differences that can be ascribed to situations. Nor the two tests that occurred without an active prototype, nor the tests where the device was actively used show noteworthy distinctions amongst the proposed categories.

Unfortunately, a defect occurred in collecting video footage during the test without a prototype. Therefore, the footage of this test is deemed inadmissible for further analysis and will not be included in further evaluation. However, as the test without a prototype and the test without an active prototype have been categorized similarly based on elapsed time, it is postulated that the number of steps and freezing episodes will be comparable as well.

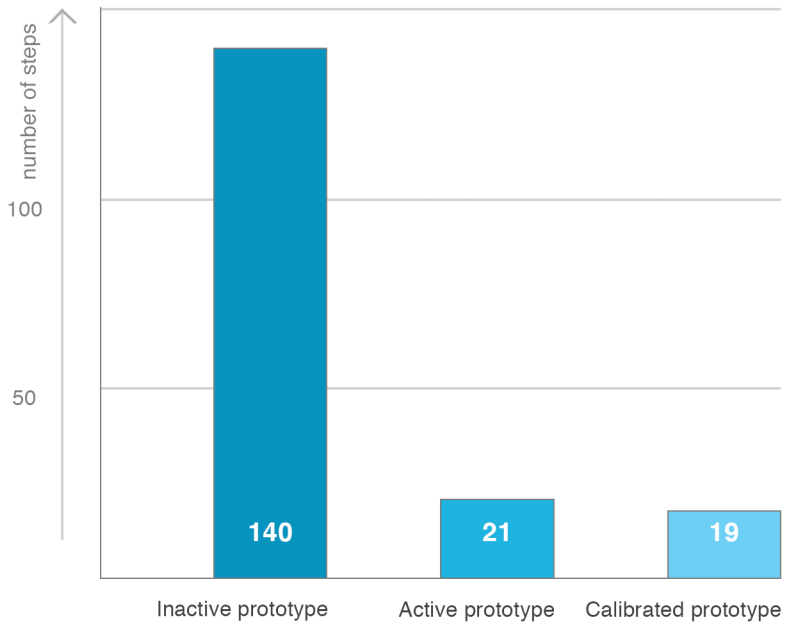

Figure 11: *The number of steps needed to complete the trajectory plotted against the different situations*

The number of steps taken during testing shows a division similar to the one found previously, regarding the elapsed test time, as is illustrated in Figure 11. The number of required steps to traverse the trajectory was reduced rather abruptly when the device was activated. Likewise, the difference between the results using calibrated prototype and the regular active prototype are small.

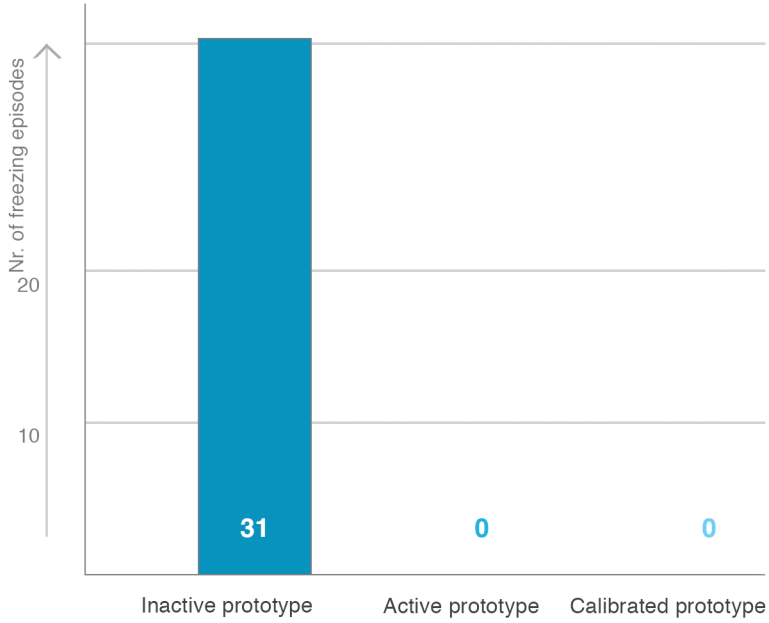

Figure 12: *The number of freezing episodes that occurred during testing plotted against the different testing situations*

The last studied parameter is the number of freezing episodes that occurred during testing and is depicted in Figure 12. Like the previous studied parameters, a clear difference can be seen between the categorized testing situations. Moreover, the freezing episodes were eliminated altogether when the device was activated.

The discovered results are summarized in **table 1**.

Table 1: *summarized results of the preliminary test*

Situation	Elapsed time (min)	Number of steps	Number of freezing episodes
Without prototype	4:30		
Inactivated prototype	4:12	140	31
Active prototype	0;14	21	0
Calibrated prototype	0:12	19	0

Conclusion

The TUG test showed a substantial patient response to the active prototype. Walking speed increased, while the number of required steps to traverse the trajectory was reduced and freezing episodes were absent entirely. Calibration of the device did increase walking abilities slightly. However, this effect was not striking and may have been generated by the test-enhanced learning effect.

The device's mechanism of action proved to be satisfactory. However, functionality posed an inconveniency. Signal transmission was not optimal and should be enhanced for ideal functionality.

4.5 REFINED CONCEPT

CHAPTER 5: CONCLUSION

The primary research question posed in this paper was to establish feasibility of the working principle of the tactile cueing device intended to combat gait impairments caused by Parkinson's disease, by formulating the following main research question:

Is it feasible to oppose gait impairments deriving from Parkinson's disease effectively by using a tactile-based cueing device?

5.1 SOLVING SUB QUESTIONS

To establish whether this fundamental question is answered by this research paper, the conclusions of the sub questions will be examined and a definitive response will be compiled.

Establishing a clinical image

Which methods are conceivable to combat gait impairments caused by Parkinson's disease?

This research question proved to be essential in describing the theory behind the studied disorder and the accompanying motor symptoms. The progressive neurological ailment and possible solution pathways were examined to substantiate the intended operative method of the medical device. No common effective method has yet been established to oppose gait impairments, and the amelioration of walking related motor deficiencies could greatly enhance quality of life for PD patients. Therefore, the need for this research was validated.

Formulating a research protocol

How can the effectiveness of the product be measured?

The goal of this research section was to formulate a medical scientific protocol suitable to test the feasibility of the intended medical operation technique. Technical literature was analysed to find an appropriate testing methodology. The threefold testing approach is an appropriate technique, fitting the proof of principle character of this research.

The application for a LMR dispensation, a necessity for medical scientific research of this calibre, an unforeseen verdict was issued by the METC. Permission to commence this study without full examination was not granted. Therefore, the intended study with the PD patients could not be performed.

Optimizing prototype design

In what way should the current prototype be altered?

After an analysis of the existing prototype, new design requirements were formulated. Implementing these requirements, an Arduino device was developed which contained all desired functionality. Several design phases were required to establish a prototype that was deemed to be appropriate. The design process was supported by a preliminary test used to asses prototype functionally. A noteworthy improvement of walking abilities occurred when the PD subject was exposed to the functional device, and the last adjustments were made. The device was hereafter considered to be appropriate for medical scientific research.

Implications of use test

What are the implications of the use test on the feasibility of the potential of the cueing device?

This research question was formulated to describe the completed use test and its implications. However, as mentioned in section 5.2, the intended study could nog legally be performed and is therefore omitted. Consequently, no answer to this sub question could be formulated.

5.2 MAIN RESEARCH QUESTION

To conclude, abovementioned solutions to the sub questions will be bundled to see if an answer to the main research question is possible.

Is it feasible to oppose gait impairments deriving from Parkinson's disease effectively by using a tactile-based cueing device?

The unexpected METC verdict impeded the performance of a patient study. This study would have been essential in establishing feasibility of the effectiveness of the prototype. Therefore, the main research question cannot be answered.

However, it is noteworthy that the potential of the designed cueing technique is substantiated by this research. Both executed literature study and the preliminary test are promising.

CHAPTER 6: RECOMMENDATIONS

The results of this research allow for an official medical scientific study. The protocol and prototype obtained in this research are appropriate to test the feasibility of the proposed working mechanism. As the preliminary test was a notable success, it is recommended to continue this research following the official path provided by the METC. Thereby obtaining permission to perform this research by applying for a positive LMR assessment.

As this research is promising, the eventual results of the proof of principle study are intended to lay ground for a scientific manuscript that will be offered to peer-reviewed journal.

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APPENDIX 1: PROEFPERSONENINFORMATIE VOOR DEELNAME AAN MEDISCH-WETENSCHAPPELIJK ONDERZOEK

Verbetering van het loopvermogen van Parkinsonpatiënten

Geachte heer/mevrouw,

Ik vraag u om mee te doen aan een medisch-wetenschappelijk onderzoek met als doel het loopvermogen te verbeteren van patiënten met de ziekte van Parkinson. Uw deelname is geheel vrijwillig; voor deelname is wel uw schriftelijke toestemming nodig. U wordt gevraagd om deel te nemen aan dit onderzoek aangezien u de ziekte van Parkinson heeft en bij u een verminderd loopvermogen is gevonden.

Voordat u beslist of u wilt meedoen aan dit onderzoek, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de onderzoeker uitleg als u vragen heeft. U kunt ook een van de betrokken specialisten om aanvullende informatie vragen, zij worden aan het eind van deze brief genoemd. Daarnaast kunt u er ook over praten met uw partner, vrienden of familie.

Algemene informatie
Dit onderzoek wordt uitgevoerd door een onderzoeker van de Universiteit Twente, in samenwerking met het Medisch Spectrum Twente. Naar verwachting zullen er ongeveer 8 proefpersonen meedoen.

Wat is het doel van het onderzoek?
Het doel van dit onderzoek is uitzoeken hoe effectief een nieuw medisch hulpmiddel is, in het verbeteren van het loopvermogen. Dit onderzoek is de eerste stap in de ontwikkeling van een product dat personen met de ziekte van Parkinson kan helpen gemakkelijker zelfstandig te lopen. Uiteindelijk is het doel patiënten te helpen zelfstandigheid en mobiliteit te behouden.

Hoe wordt het onderzoek uitgevoerd?
Als u heeft toegezegd deel te willen nemen aan het onderzoek, zal de onderzoeker eerst kort vragen naar uw medische geschiedenis. Vervolgens wordt u gevraagd mee te doen aan twee korte looptesten. Beide testen zijn bedoeld om te kijken wat uw huidige loopvermogen is, en of het product ervoor zorgt dat u gemakkelijker kan lopen.

- Bij de eerste test wordt u een aantal keer gevraagd om op te staan uit een stoel, drie meter te lopen en vervolgens opnieuw in de stoel te gaan zitten.
- Voor de tweede test wordt u gevraagd om tien meter te lopen. Eerst twee keer zoals u normaal zou lopen, en vervolgens ook twee keer met een bekertje water in uw hand.

Als laatste wordt u gevraagd of u het idee heeft dat het product ervoor zorgt dat u beter kon lopen. Er vindt geen verder vervolgonderzoek plaats.

Wat zijn de mogelijke voor- en nadelen van deelname aan dit onderzoek?
Als deelnemer heeft u geen direct langdurig voordeel bij deelname aan dit onderzoek. Ook als u direct verlichting van symptomen ervaart kun u het product niet mee naar huis nemen. Op lange termijn kan dit onderzoek bijdragen aan het op de markt brengen van een loophulpmiddel. Als

u deelneemt aan dit onderzoek wordt u gevraagd tijd vrij te maken voor bovengenoemde tests.

Wat zijn de risico's van deelname aan dit onderzoek?
Als u deelneemt aan het onderzoek loopt u dezelfde risico's als bij uw gebruikelijke dagelijkse handelingen. De handelingen die u gevraagd wordt uit te voeren zijn minimaal belastend en eenvoudig. Om de kans op ongewenste situaties zo klein mogelijk te houden mag u gebruik maken van eigen dagelijkse loophulpmiddelen, zoals een stuk of een rollator. Ook zal de onderzoeker naast u meelopen om u op te vangen indien u valt.

Wat gebeurt er als u niet wenst deel te nemen aan dit onderzoek?
U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u niets te tekenen en ook niet te zeggen waarom u niet wil meedoen. Dit heeft geen consequenties.

Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen, ook tijdens het onderzoek. U hoeft niet te zeggen waarom u stopt.

Als er nieuwe informatie over het onderzoek is die belangrijk voor u blijkt, laat de onderzoeker dit weten. U wordt dan gevraagd of u blijft meedoen.

Wat gebeurt er met uw gegevens?
Al uw gegevens zijn vertrouwelijk. Alleen het onderzoeksteam heeft toegang tot deze gegevens. Uw gegevens worden doorgegeven aan de opdrachtgever van het onderzoek (Universiteit Twente) maar nooit onder vermelding van uw naam of andere persoonsgegevens.

Uw gegevens kunnen worden bewaard om later gebruikt te worden voor verdere stappen in dit onderzoek. Mocht u hier bezwaar tegen hebben kunt u dat aangeven bij het inleveren van het toestemmingsformulier.

Heeft u verder nog vragen?
Als u besloten heeft deel te nemen aan dit onderzoek, wordt u gevraagd dit op het toestemmingsformulier schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek.

Mocht u nog verdere informatie willen hebben of andere vragen hebben, kunt u contact opnemen met het onderzoeksteam. Ook bijzonderheden of problemen gedurende het onderzoek kunt u melden via deze contactgegevens.

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Bijlagen
Bijlage 1: Toestemmingsformulier proefpersoon

Bijlage 2: Anamnese
Bijlage 3: Schaal globaal ervaren effect

BIJLAGE 1: TOESTEMMINGSFORMULIER PROEFPERSOON

Verantwoording onderzoeker:

Ik heb mondelinge en schriftelijke toelichting gegeven op het onderzoek. Resterende vragen over het onderzoek zal ik naar vermogen beantwoorden. De deelnemer zal van eventuele voortijdige beëindiging van deelname aan dit onderzoek geen nadelige gevolgen ondervinden.

Naam onderzoeker:

Handtekening: Datum: ___/___/_____

Informed consent deelnemer:

Ik verklaar op een voor mij duidelijke wijze te zijn ingelicht over de aard, methode, doel, risico's en belasting van het onderzoek. Ik weet dat de gegevens en resultaten van het onderzoek alleen anoniem en vertrouwelijk aan derden bekend gemaakt zullen worden. Mijn vragen zijn naar tevredenheid beantwoord. Ik stem geheel vrijwillig in met deelname aan dit onderzoek. Ik behoud me daarbij het recht voor om op elk moment zonder opgaaf van redenen mijn deelname aan dit onderzoek te beëindigen.

Naam deelnemer:

Handtekening: Datum: ___/___/_____

☐ *Ik heb er bezwaar tegen dat mijn gegevens worden bewaard en eventueel, na mijn toestemming,*

voor een ander (vervolg)onderzoek gebruikt kunnen worden.

BIJLAGE 2: ANAMNESE

Anamnese afgenomen op (datum):

Anamnese afgenomen door:

Leeftijd:

Geslacht:

Aantal jaar sinds de diagnose Parkinson:

Score op de Hoehn en Yahr schaal:

Staat van medicatie (ON/OFF):

In uw slechtste staat/op uw slechtste moment, loopt u:
- ☐ 1. Normaal
- ☐ 2. Bijna normaal ... een beetje langzaam
- ☐ 3. Langzaam maar volledig zelfstandig
- ☐ 4. Met assistentie of een loophulpmiddel
- ☐ 5. Niet in staat te lopen

Beïnvloeden uw loopproblemen uw dagelijkse activiteiten en onafhankelijkheid?
- ☐ 1. Helemaal niet
- ☐ 2. Enigszins
- ☐ 3. Matig
- ☐ 4. Ernstig
- ☐ 5. Niet in staat om te lopen

Heeft u het gevoel dat uw voeten vastgenageld staan aan de vloer wanneer u loopt, draait of wanneer u start met lopen (freezing)?
- ☐ 1. Nooit
- ☐ 2. Heel soms: ongeveer eens per maand
- ☐ 3. Soms: ongeveer eens per week
- ☐ 4. Dikwijls: ongeveer eens per dag
- ☐ 5. Altijd: altijd wanneer u loopt

Hoe lang duurt uw langste periode van freezing?
☐ 1. Nog nooit gebeurd
☐ 2. 1 tot 2 seconden
☐ 3. 3 tot 10 seconden
☐ 4. 11 tot 30 seconden
☐ 5. Meer dan 30 seconden niet in staat om te lopen

Hoe lang duurt uw periode van aarzeling bij het starten meestal? (freezing bij zetten van de eerste stap)
☐ 1. Geen
☐ 2. Het duurt meer dan 1 seconde om te starten met lopen
☐ 3. Het duurt meer dan 3 seconden om te starten met lopen
☐ 4. Het duurt meer dan 10 seconden om te starten met lopen
☐ 5. Het duurt meer dan 30 seconden om te starten met lopen

Hoe lang duurt uw aarzeling bij het draaien meestal? (freezing tijdens het draaien)
☐ 1. Geen
☐ 2. Het draaien wordt na 1 tot 2 seconden hervat
☐ 3. Het draaien wordt na 3 tot 10 seconden hervat
☐ 4. Het draaien wordt na 11 tot 30 seconden hervat
☐ 5. Meer dan 30 seconden niet in staat om het draaien te hervatten

APPENDIX 2: ONDERZOEKSPROTOCOL

Achtergrond van het onderzoek
Een verminderd loopvermogen is veelal een sterk aanwezig onderdeel van het klinische beeld van de ziekte van Parkinson. Dit symptoom heeft niet alleen grote fysieke gevolgen voor de patiënt, maar heeft ook zijn weerslag op mobiliteit en sociaal functioneren. De afname van het loopvermogen wordt op lange termijn in verband gebracht met een breed scala aan symptomen en heeft uiteindelijk een grote invloed op de ziekteprogressie. Onderzoek wijst uit dat patiënten met de ziekte van Parkinsons gevoelig zijn voor het fenomeen kinesia Paradoxa, het vermogen van een akinetisch persoon om plotselinge verlichting van mobiliteitsproblemen te ervaren.

Onderzoeksvraag
Dit onderzoek is opgezet middels de proof of pinciple methode. In dit geval wordt gepoogd aannemelijk te maken dat de beoogde methode van cueing het gewenste effect op het loopvermogen van patiënten met de ziekte van Parkinson kan hebben. De bijbehorende vraagstelling luidt als volgt:

Is het aannemelijk dat een verminderd loopvermogen, als gevolg van de ziekte van Parkinson, verbeterd kan worden door gebruik te maken van een device?

Deze vraag zal beantwoord worden aan hand van de gegevens verkregen middels dit onderzoek. Het antwoord op de onderzoeksvraag wordt niet alleen gebaseerd op de benodigde tijd om het voorgelegde loopparcours af te leggen, maar ook op staplengte, aantal freezing momenten en patiënt ervaring.

Om een verbetering te kunnen waarnemen worden in dit onderzoek twee condities vergeleken, namelijk het loopvermogen mét cueing device en het loopvermogen zonder cueing device.

Patiënt populatie
De voornaamste factor die patiënt geschiktheid voor het onderzoek bepaald is het ervaren van een verminderd loopvermogen als gevolg van de ziekte van Parkinson.

Patiënten worden uitgesloten van deelname indien zij:
- Minderjarig zijn
- Dusdanig cognitief beperkt worden dat zij het onderzoek en bijbehorende instructies niet kunnen begrijpen
- Een verminderd loopvermogen ervaren met een andere oorzaak dan de ziekte van Parkinson

Het onderzoek zal uitgevoerd worden met een kleine groep poliklinische patiënten. Zij zullen door de behandeld arts tijdens een reguliere afspraak gevraagd worden of zij bereid zijn mee te werken aan dit onderzoek. Indien de patiënt toezegt interesse te hebben wordt de informatiebrief voor proefpersonen aangeboden. Als deze volledig is doorgenomen is er nog ruimte voor eventuele

vragen, en vervolgens wordt de patiënt geraagd definitief toe te zeggen of hij/zij wil deelnemen aan het onderzoek. Indien de patiënt bereid is tot deelname kan het onderzoek direct van start gaan. Na deelname vindt er geen vervolgonderzoek plaats.

Onderzoeksopzet

Het onderzoek is opgezet aan hand van drie korte, minimaal belastende gestandaardiseerde tests.

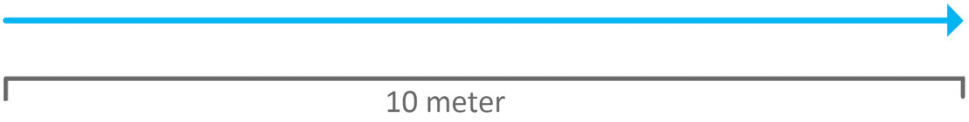
1. Allereerst wordt een korte anamnese afgenomen bij de patiënt om een beeld te krijgen van het ziekteverloop en de mate van loopritmestoornissen. De gegevensverwerking van de verkregen informatie zal volledig anoniem plaatsvinden.
2. Vervolgens zal er een gestandaardiseerde Timed UP and GO (TUG) test plaatsvinden

Deze test zal driemaal worden uitgevoerd

   a. Eenmaal om het reguliere loopvermogen van de patiënt vast te stellen
   b. Nogmaals om te kijken of het niet-geactiveerde device een effect heeft op de loopstoornis
   c. Vervolgens om het effect van het device op het loopvermogen vast te stellen

3. De patiënt zal vervolgens gevraagd worden om de 10 meter looptest uit te voeren

In de eerste fase zal de test drie keer plaatsvinden:



   a. Eenmaal om het reguliere loopvermogen van de patiënt vast te stellen
   b. Nogmaals om het effect van het device op het loopvermogen vast te stellen
   c. Vervolgens om te kijken of het niet-geactiveerde device een effect heeft op de loopstoornis

Vervolgens zal de test nog driemaal worden uitgevoerd, waarbij de patiënt gevraagd zal worden om een bekertje met water bij zich te dragen.

   d. Eenmaal om het reguliere loopvermogen van de patiënt vast te stellen, waarin de aandacht van de patiënt verdeeld is.
   e. Nogmaals om te kijken of het niet-geactiveerde device een effect heeft op de loopstoornis bij multitasking
   f. Vervolgens om het effect van het device op het loopvermogen vast te stellen wanneer de aandacht van de patiënt verdeeld is

De uitvoering van test 2 en 3 zal vastgelegd worden door middel van video opnames. Aan hand daarvan wordt door twee onderzoekers onafhankelijk het aantal stappen en freezing momenten bepaald. Het beeldmateriaal zal in een beveiligde omgeving bewaard worden, en zal alleen toegankelijk zijn voor het onderzoeksteam.

De primaire uitkomstmaten waarop en antwoord op de onderzoeksvraag gebaseerd wordt zijn als volgt:

- Tijd benodigd voor de patiënt om de loopparcoursen af te leggen
- Staplengte en aantal freezing momenten gedurende de looptesten
- Ervaring van de patiënt, zoals gevonden door het invullen van de waarderingsschaal

APPENDIX 3

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APPENDIX 4

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APPENDIX 5

APPENDIX 6

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APPENDIX 7