General introduction

Most of us walk with remarkable efficiency and don’t give it another thought. However, walking can become more challenging or even impossible when the motor control or musculoskeletal system is impaired. Since the ability to walk is an important requirement for many daily-life activities, these gait limitations can have a major impact on a person’s activities and participation in society. Therefore, rehabilitation medicine aims to preserve or improve walking capacity by thoroughly measuring and correcting for abnormal human movement. Several treatments are available to achieve this goal and physical examination and clinical gait analysis are commonly used instruments to assess a patient’s impairments to aid treatment selection.

One of the disorders in which walking problems frequently occur is cerebral palsy (CP), which is a motor disorder that results in a wide variety of impairments and gait limitations of different severity. This heterogeneity of the CP population in combination with a range of available treatments make the selection of the optimal treatment for a specific patient a challenge. In addition, the relation between measured impairments and gait limitations is complex, with compensation strategies that obscure the recognition of true gait limitations. Therefore, advanced technologies are increasingly used to improve their identification and thus aid subject-specific treatment selection and outcome evaluation. For instance, motorized alternatives of the tests performed during the physical examination can quantify potential impairments more objectively. In addition, interactive gait labs can provide means to study the effect of impairments during normal gait and more challenging tasks to identify compensation strategies. In this thesis, the feasibility and validity of these advanced instrumented techniques that aim to clinically assess motor (dys)function in children with CP is evaluated.
Spastic cerebral palsy

Cerebral palsy is the most common cause of physical disability in childhood, occurring in one to three per 1000 live births in Europe. CP refers to a group of permanent motor disorders that affect the development of movement and posture. These disorders are the result of dysfunction in the parts of the developing fetal or infant brain that control movement, balance and posture. This dysfunction can be caused by for instance oxygen deprivation or acquired brain injury and depending on its location, patients with CP have varying problems with movement and posture. These motor problems are often accompanied by problems with sensation, perception, communication, cognition and behavior. Thus, individuals with CP form a heterogeneous population, ranging from lightly affected patients with the ability to walk independently, to severely affected patients who are bound to their wheelchair and fully dependent on their caretakers.

To categorize the impact of CP on a child’s functioning, the ICF-CY (International Classification of Functioning, disability and health for Children and Youth) is often used. This classification distinguishes the levels of body functions and structure as well as activity and participation, while it also recognizes their mutual interactions and the influence of personal and environmental factors. The activity and participation level describes the limitations in mobility, such as walking, and the impact on a patient’s daily life activities and participation in society. The level of body function and structures describes the physical impairments caused by CP.

Impairments can be distinguished into primary (or neural) impairments that are a direct result of the brain dysfunction and secondary (or non-neural) impairments that gradually develop over time. A commonly occurring primary impairment is stretch hyperreflexia, which is present in 80% of the individuals with CP. These exaggerated stretch reflexes have also been referred to as spasticity, although there is no consensus on the exact definition of spasticity in literature. Spastic CP is typically characterized by an increase in joint resistance to motion, i.e. hyper-resistance. However, there are other impairments than hyperreflexia that can also cause hyper-resistance. Next to spastic CP, there are also dyskinetic (10% of the patients) and ataxic (5-10% of the patients) CP, which are characterized by involuntary movements and incoordination or shaky movements, respectively.

Other primary impairments include hyper-excitability of other reflexes than the stretch reflex, such as postural reflexes and released flexor reflexes (a withdraw reflex from painful stimuli), as well as hypertonia and poor selective motor control. Hypertonia is here defined as velocity-independent increased resistance to passive movement caused by excessive background muscle activation. Poor selective motor control is to a reduced ability to recruit a specific muscle group to move a joint independently from other joints and can result in synergistic or mirror movement patterns, excessive co-contraction and a loss of dexterity. In contrast to these excessive responses, there are also deficit impairments, such as muscle paresis. Paresis refers to muscle weakness due to a decreased number of effective motor units resul-
ting from a decreased cortical input. The exact mechanisms underlying these primary impairments in CP remain uncertain, although disruption of different inhibitory and excitatory mechanisms at the spinal cord and muscle level have been described (for more details, see Box 1-1).

As a result of abnormal muscle usage or loading of bones caused by the primary impairments, secondary impairments may gradually develop over time (Fig. 1-1). Secondary impairments that contribute to hyper-resistance include shortened muscles that restrict the range of motion of a joint, increased tissue stiffness (or viscoelasticity) of the muscle-tendon unit and surrounding tissue, increased intrinsic stiffness due to an increased number or formed cross-bridges and a reduced detachment rate during stretch. The exact pathophysiology behind these secondary impairments is complex. Amongst the suggested changes are a reduction in the number and length of sarcomeres, change in size and type of muscle fibers, and alterations in the content of the extracellular matrix and intramuscular connections, such as increased extracellular space, collagen concentration and other fibrous connective tissue. Other secondary impairments include muscle weakness as a result of reduced use (atrophy) and deformations of the bone or joint. The latter can in turn affect the function of bones as lever arms.

Together, these primary and secondary impairments can result in different gait impairments (Fig. 1-1). These can include for instance reduced range of motion of different joints, abnormally high muscle co-contraction, reduced push-off, untimely muscle activation and increased energy cost. It has also been shown that task-specific modulation of the excitability of stretch reflexes is reduced, thus reducing the functionality of these reflexes to control gait.

Fig. 1-1. Overview of some of the restrictions, limitations and gait impairments as well as their underlying impairments, categorized according to the ICF-CY model (in gray). Primary impairments are the direct result of the brain lesions and often lead to development of secondary impairments over time. Together these impairments affect the muscle activity during gait, resulting in altered joint kinematics and kinetics. These gait deviations in turn can result in limited walking performance and thus restrictions on the participation level.
To categorize the resulting motor functioning, different classifications are used. The severity of (gross) motor limitations can be classified according to the GMFCS (Gross Motor Function Classification System), which consist of five different levels. Children with level I and II walk independently without walking aids, children with level III walk with a walking aid and children with levels IV and V are unable to walk. However, this measure is not really specific in discriminating between ambulant patients (generally level I-III). Different classifications are available in literature to describe common gait deviations in CP (Box 1-2).
vations during the stance phase are toe walking (equinus gait), knee hyperextension (knee recurvatum), and excessive flexion of both knee and ankle (crouch gait). During swing, the patient can be unable to sufficiently lift their foot (drop foot) or flex their knee (stiff knee gait).

About 70% of children with CP are able to walk (in)dependently. Still, most of these ambulatory children struggle with limitations of their gait, such as a reduced walking speed and walking distance, and frequent falling. Since the ability to walk is an important requirement for many daily-life activities, these limitations can have a major impact on a patient’s level of participation in society, such as restrictions in for instance playing outside. These limitations are therefore often part of patient needs and thus a main goal of treatment. To achieve this, treatments typically target the underlying impairments of gait limitations. The heterogeneity of the CP population, both in types of gait deviations, combination of underlying impairments and compensation strategies, together with the diversity of available treatments make the selection of the optimal treatment for a specific patient a challenge. Moreover, the underlying impairments are not constant but ever changing with growth, maturation, learning and treatment. Even though the interplay between all factors makes it difficult, a good identification of the underlying causes is an important step to optimally treat a patient.

Current assessment

Unfortunately, to date CP cannot be cured. Instead, the different available interventions aim to preserve or improve posture and gait by targeting the underlying impairments and to oppose (further) development of secondary impairments. A variety of treatments is available, ranging from home stretching programs, physiotherapy, orthopedic footwear and orthotics, to orthopedic surgery and neurosurgical or pharmacological treatment of stretch hyperreflexia. Physiotherapy generally aims to support the motor development and improve strength and endurance. Orthopedic footwear and orthotics are used to control the position and motion of primarily the more distal joints, while orthopedic surgery corrects for secondary impairments, such as bony deformations and shortened muscles. Neurosurgical or pharmacological treatment of stretch hyperreflexia is aimed at increasing a child’s ability to walk and to prevent (further) development of contractures or deformations in children with GMFCS levels I-III. In the more severe patients, this treatment is more focused on pain reduction and improving their ability to sit or to relieve their caretaking.

Reduction of stretch hyperreflexia is a common goal for which different treatments are available. For general reduction of stretch reflexes, there exists oral antispasticity medication such as Diazepam, Baclofen and Dantrolene. A more localized alternative consist of intramuscular injections with Botulinum NeuroToxin (BoNT), which causes a temporal chemical denervation and weakening of the treated muscles. Often, this treatment is combined with serial casting or physiotherapy, in order to stretch shortened muscles. Neurosurgical options such as an intrathecal baclofen (ITB) pump or selective dorsal rhizotomy (SDR) offer a more permanent
Box 1-2: overview of normal gait (left) and typical gait deviations in CP based on descriptions by Rodda et al. and Becher et al.. Many patients seem to be walking on their toes. This ‘toe walking’ can be subdivided into different patterns. First, in less severely affected children, there can be heel rise at mid-stance with normal knee extension (true equinus gait) or knee hyper extension (equinus knee recurvatum – both Becher’s type 3). The moment during the gait cycle the heel rise occurs can differ (not shown), with heel lift starting just prior to mid-stance (early heel rise) or during the whole stance phase (true toe walking). In addition, severely affected children often walk with excessive knee flexion throughout stance in combination with heel rise (equinus jump gait – Becher’s type 4). There are also patients who walk with excessive knee flexion but with a neutral ankle angle (apparent equinus). Next to toe walking, patients can walk with knee hyperextension after initial contact without heel rise (knee recurvatum – Becher’s type 2). This can be accompanied by insufficient foot lift during swing and insufficient knee extension in terminal swing. The opposing pattern commonly occurs, with excessive knee flexion in mid-stance without heel rise (crouch gait – Becher’s type 5). The severity of this pattern depends on the degree of flexion in hip, knee and ankle, and can be a mild deviation or a severe deviation with risk of loss of walking ability. During swing, an inability to lift the foot can occur in mildly affected children, resulting in increased ankle plantar flexion during swing (drop foot) and leading to a forefoot landing at initial contact (Becher’s type 1). In addition, the inability to flex the knee during swing (stiff knee gait) does also occur. It should be noted that the terminology and exact definitions vary in the literature. These gait classifications only describe common gait deviations in the sagittal plane (side view), however, they typically coincide with deviations in the other planes, such as hip rotation and hip and pelvic lift.

treatment option. ITB reduces the excitability of the reflex pathway within the spinal cord while the pump allows for controlled and localized administration. Finally, SDR consists of cutting a portion of dorsal nerve roots in the spinal cord to reduce sensory afferent input. Thus, several treatments and combinations thereof are available to improve mobility in ambulant patients, targeting different impairments. Therefore, treatments should be selected that match the patient’s needs and underlying impairments. In order to achieve this, objective measurement of these impairments is imperative. Currently, physicians rely on the results of physical examination as well as clinical gait analysis. During the physical examination, manual tests are performed that give an indication of increased resistance to stretch and the main underlying impairments, i.e. stretch hyperreflexia and muscle stiffness. The gait analysis in turn can indicate whether these impairments seem to be affecting a patient’s gait pattern. For instance, when both increased tissue stiffness and stretch hyperreflexia are suspected based on
physical examination, clinical gait analysis is used to determine whether stretch hyper-reflexia seems to be negatively affecting gait. If this is the case, BoNT combined with casting can be considered. However, if the hyperreflexia does not seem to affect gait or if the resulting increased joint resistance is necessary to walk, only casting should be considered or no treatment at all.

Thus, physical examination is used by clinicians to help them find suspected primary and secondary impairments in patients. Common tests to assess stretch hyperreflexia are the Modified Ashworth Scale, Modified Tardieu Scale and the Spasticity Test (SPAT). The principle of these tests is that the examiner imposes a passive stretch on a joint and rates the perceived resistance, while the patient is asked to relax. During slow stretch, a reduction in range of motion is indicative of shortened muscles and increased tissue stiffness. A difference in resistance between slow and fast stretch suggests the presence of stretch hyperreflexia. Although this information is used to support clinical decision making, these tests have several major shortcomings. First, the execution of the movements and rating of the resistance differs between examiners and repetitions, i.e. the tests are subjective and the interpretation can be inaccurate. In addition, these measurements can be affected by the posture of the limb, sensory stimulation and factors such as previous activities or stress. Third, the resolution of the tests is not sensitive enough to intervention or development over time. Lastly, the tests are not able to correctly differentiate between the primary and secondary impairments that underlie hyper-resistance of a joint.

Fig. 1-2. A simplified overview of treatment selection aimed at improving gait. First, the patient needs are assessed, which are usually related to gait limitations. Then, during the physical examination, the impairments that are most likely causing the hyper-resistance of a patient’s lower joints are identified. Note that this simplified scheme focuses on two main causes, increased tissue stiffness (dotted line), stretch hyperreflexia (solid line) and a combination thereof (dashed line), whereas other causes such as orthopedic problems are not taken into account. In addition, only a few treatments are included in this overview. During gait analysis, it is examined whether the identified hyperreflexia does (=) or does not (≠) have a negative effect on gait. This results in an “optimal” treatment option, or no active treatment in case of suspected hyperreflexia that does not interfere with gait or coexist with increased tissue stiffness. The final treatment plan, however, is the result of a more complex consideration, that also takes into account other medical problems, allergies, patient’s prospect and preference as well as those of an under-aged patient’s caretakers.
This suggests that the selection of therapies is currently not well informed, and therefore a more objective and quantitative hyper-resistance assessment is required.

Gait analysis is performed complementarily to the physical examination, to evaluate the effect of suspected impairments on gait. Gait analysis can consist of simple video recordings to register movements which can later be reviewed and analyzed by clinicians. Alternatively, more thorough examination consist of 3D measurement of body movement by tracking the motion of markers that are attached to the body by optical motion analysis systems. This allows for calculation of kinematics that quantitatively describe abnormalities in the movement pattern on the level of segment and joint angles. Kinematics and ground reaction forces can in turn be used to calculate kinetics. The resulting net joint moments and powers give an indication of the cause of the movement abnormalities and the relation with underlying muscle function. To gain insight into the role of individual muscles during gait, muscle electromyography (EMG) signals can be recorded using surface electrodes mounted on the skin. EMG signals represent the electrical activity of muscles and thus provide insight into the coordination of different muscle groups (e.g. selectivity and co-contraction) and abnormal activity patterns (e.g. stretch hyperreflexia). While the current technological systems allow for objective and quantitative measurement of gait, they require specious laboratories, are limited to the measurement of only a few consecutive strides while it is cumbersome to measure multiple strides with correct foot placement on the force plates. Also, measurement are limited to normal gait and patients have to be cooperative to perform gait analysis.
Advanced technologies

Different alternative technologies have been developed to address the mentioned drawbacks of both physical examination and gait analysis. First, motorized hyper-resistance tests allow for standardized physical examination and thus provide objective and quantitative information. This opens the door for neuromuscular modelling to provide more insight into the underlying impairments. Second, an interactive gait lab could provide ways to measure patient’s outside their optimal walking pattern to discern between the compensation strategies and the effect of impairments on gait. Third, features of the interactive gait lab, such as treadmill perturbations, can be used to perform physical examination tests directly during gait. Each of these three forms of novel technologies will be introduced below.

1. Motorized hyper-resistance test

Instrumented versions of the physical examination tests to measure stretch hyper-reflexia have recently been introduced. They measure the resistance to an imposed passive movement, using for instance inertial sensors and a force transducer, and relate the resistance to muscle activity measured with EMG. It has been demonstrated that these instrumented tests considerably improve the objectivity and precision of the hyperreflexia measurements. In addition, the quantitative data allows for the use of neuromuscular models to gain better understanding of the underlying mechanisms. These tests, however, do not control for the force that is applied during the movement or velocity of the stretch, while stretch hyperreflexia is considered to be both force- and velocity-dependent. In addition, it is unknown to what extent the measurements are influenced by the applied movement profile and interactions between patient and examiner during the movement.

An alternative to the manually applied movements is the use of robotic designs, in which a motor-driven system manipulates the joint in a controlled manner (Fig. 1-3). A motorized foot plate rotates the ankle through its range of motion. Thus, the hyper-resistance tests can be performed in a standardized way, using ramp-and-hold rotations or any other movement profile. In addition, small perturbations can be applied on top of this movement, that allow for more in-depth analysis of the underlying impairments. Finally, instead of passive conditions, the tests can be combined with visual feedback to measure under active conditions, such as retaining a certain contraction level or moving the foot.

Several studies have already used these motorized assessments. Some compared the measured resistance during slow with fast movements, using similar assumptions as with the manual measurements. Alternatively, passive stiffness parameters have been derived from the torque-angle relation measured during slow movement while reflex properties were estimated from EMG signals recorded during tendon tapping. Together, these approaches have shown that spastic patients generally have increased reflex activity and tissue stiffness and that the reflex activity decreases after treatment. More advanced analysis started with the application
of biomechanical models to estimate tissue stiffness \(^68,69\). Later, non-linear models combined with system identification and parameter estimation techniques were introduced \(^70-75\), which integrated both tissue and reflex components to accurately untangle their contributions. In addition, the non-linear nature of the models allowed for analysis over large angular displacements or torque differences that are common during normal movement such as gait. Using these non-linear models, tissue stiffness and reflex activity have been found to be elevated in spastic stroke and spinal cord injury patients \(^70-73,75\). However, the applicability of motorized resistance tests combined with these advanced analyses has not yet been examined in children with and without CP.

2. Interactive gait lab

As an alternative to standard gait analysis, interactive gait labs are increasingly used in gait analysis laboratory settings (Fig. 1-4). They consist of instrumented, feedback-controlled treadmills that allow subjects to continuously control and inherently select the belt speed, so called self-paced (SP) walking. Instrumented treadmills have integrated force plates that allow them to measure ground reaction forces during many consecutive strides while requiring a small laboratory space. In addition, they come with an immersive virtual reality (VR) environment. The self-paced walking, relative large size of the belts and the visual flow provided by the VR environment are used to imitate real-life walking \(^76,77\) in order to reduce differences in gait pattern from normal overground walking that have been reported for conventional treadmills \(^77-81\).

In addition, self-paced walking does not require protocols to establish the preferred walking speed prior to setting a fixed speed on a conventional treadmill and it also allows for measurement of long term gait variability or fatiguing. The VR environment can be used to provide real-time feedback to a patient \(^82\) to improve gait or to provide challenging tasks to get a patient out of his or her comfortable walking pattern. In addition, it can alsobe used to distract a patient to measure a more representative gait pattern, or to improve the enthusiasm and collaboration of a child during the measurements. Finally, these treadmills allow for different mechanical manipulations of gait, including sudden external perturbations by pitch or sway of the treadmill and external pull systems to examine gait stability \(^83,84\), split-belt speed differences to study adaptation of motor behavior \(^85\), and small belt accelerations to study reflexes and ankle stiffness \(^86,87\). Thus, interactive gait labs offer ways for additional, insightful clinical measurements while improving the collaboration of children.

Before these interactive labs can be used for clinical measurements, they should be compared against conventional gait analysis. First, the technical prerequisites should be checked to determine whether the accuracy of the force signals recorded by instrumented treadmills are adequate for gait analysis. Second, the effect of the different modalities, i.e. walking with VR and at SP, on the gait pattern of healthy subjects should be determined. Finally, it is unknown if SP and VR walking are feasible in children with CP, and whether treadmill-based clinical gait analysis is comparable to conventional overground gait analysis.
Introduction

3. Functional hyper-resistance test

Although the motorized hyper-resistance test is performed in a controlled manner, it is executed while the patient is relaxed. The actual contribution of these passively measured exaggerated reflexes to gait deviations is subject of debate. On one hand, studies have found an impaired inhibition of the H-reflex during the stance phase of gait, as well as increased muscle activity in the plantar flexor muscles during muscle lengthening and the loading response specifically in children with CP, which is suggested to reflect stretch hyperreflexia. Therefore, anti-spastic treatments are frequently administered with the aim to reduce muscle hyperactivity and to facilitate, depending on the specific gait pattern, heel strike, ankle dorsiflexion and knee extension at terminal swing. However, it is not possible to dissociate spinal drive from sensory feedback mechanisms when measuring muscle activity, so these increases can also reflect the necessity of increased muscle activation to correct for increased joint stiffness. Indeed, several studies have shown that joint stiffness is increased during gait in patients with CP and that muscle paresis and passive joint stiffness are the main determinants of gait limitations. This notion is supported by several studies that found no or only mild correlations between passive spasticity measurements and gait. Other studies, however, did find a relation between passively measured stretch hyperreflexia and reduced knee angular velocity and peak muscle lengthening during faster gait. Thus, there is a need for evaluation of these impairments and their relation to gait deviations directly during walking in children with CP, which would give estimated neural and tissue characteristics that are more representative of the problems underlying activities in daily life.
Different experimental approaches have been used to evoke stretch reflexes of the lower leg muscles during gait, ranging from hammer tests that tap the tendon, electromechanical tendon vibrations, electrical stimulation of the tibial nerve, as well as functional and other electromechanical perturbations. Out of these methods, the tendon tapping, vibration and nerve stimulation are not practical and uncomfortable for patients. The functional perturbations are based on a difference in walking speeds to lengthen the muscles at different stretch velocities, which is more clinically feasible. However, it is also more complicated to discern the contribution of reflexes from the central driven muscle activation during the stance phase. Actuated joint orthoses have been used to suddenly rotate the ankle towards dorsiflexion. In different groups of spastic patients, the monosynaptic response was found to be exaggerated while its modulation was hampered. Although these actuated joints allow for reflex assessment during gait, they can also interfere with gait performance by their mass, straps and restriction in medio-lateral movement. Alternatively, sudden treadmill belt accelerations have been applied during the eighties to pull the foot backward and cause a quick stretch of the calf muscles while subjects are walking. These perturbations have been shown to result in large short-latency responses in spastic patients. Although these results seem promising, the treadmill accelerations have not been further examined or clinically implemented to date.

Aim and outline of the thesis

The general aim of this thesis is to evaluate the feasibility and validity of advanced technologies to clinically assess motor (dys)function in children with CP. These technologies include the motorized resistance test and interactive gait lab to examine the underlying factors of joint hyper-resistance and gait abnormalities to inform clinical decision making.

Feasibility and validity can be defined in different ways. Here, feasibility is defined as the suitability of instrumented measurements for the target group, i.e. young children to adolescents, with physical limitations due to CP. Validity is generally defined as the degree to which an instrument truly measures the construct it is supposed to measure. Different types of validity can be examined, for instance face, content, criterion and construct validity. The latter assess whether a measure examines every aspect of what is under investigation (content validity), whether the results correspond with a gold standard measure (criterion validity), or whether the results agree with existing knowledge and hypothesis (construct validity). Finally, reliability, is here defined as the degree to which the measure is free from measurement error, and responsiveness as the ability to detect a change over time that is not caused by measurement error.

The first part of this thesis focuses on the feasibility and validity of the motorized resistance test. In chapter 2, an extended motorized assessment protocol is presented to discriminate between soleus and gastrocnemius muscle characteristics. An ex-
tended neuromuscular ankle model was used for analysis that took the agonist into account and resulted in an estimation of stiffness as well as reflex and background activity. To examine the construct validity of the derived neural and tissue parameters, the outcomes were compared with existing knowledge of the physiology calf muscles and pathology of CP. The repeatability of the outcomes was examined as well as their responsiveness to clinical measures and treatment. As a next step in the validation process, the technique is compared to manual instrumented assessment in chapter 3.

The second part of this thesis focuses on the feasibility and validity of the interactive gait lab. First, the focus is on the technical suitability of the force data measured with instrumented treadmills for gait analysis. In chapter 4, a protocol is presented for instrumented treadmills to examine potential error sources in force and center of pressure data. To improve the force data accuracy, different calibration procedures that use an instrumented stick are examined in chapter 5. Second, the validity of the interactive gait lab for gait analysis is evaluated in healthy adults. The effects of different modes of SP walking are compared with fixed speed treadmill walking in chapter 6. The potential interaction in terms of energy exchange between treadmill and subject as a result of the SP control mechanism is described in chapter 7. The effect of a VR environment and how such an environment influences SP or fixed speed walking is examined in chapter 8. Third, the feasibility and validity of the interactive gait lab is examined for clinical gait analysis in children with CP. The effect of SP and VR relative to conventional treadmill walking is evaluated in children with CP as well as typically developing children in chapter 9. Finally, the difference between gait analysis performed in an interactive gait lab and conventional overground lab is examined in these children. In chapter 10, the differences in spatiotemporal gait characteristics and kinematics are discussed, while chapter 11 focuses on kinetic parameters.

The third part of this thesis is a first step to integrate the principle of the motorized hyper-resistance test in treadmill-based clinical gait analysis. In chapter 12 it is examined whether perturbation of the foot by belt accelerations during the stance phase of walking can evoke stretch reflexes in the calf muscles.

The main findings of these studies are discussed in their bigger context in chapter 13, after reflecting on the overall feasibility and validity of the different techniques. The clinical implications are given and recommendations are made for potential future research.

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