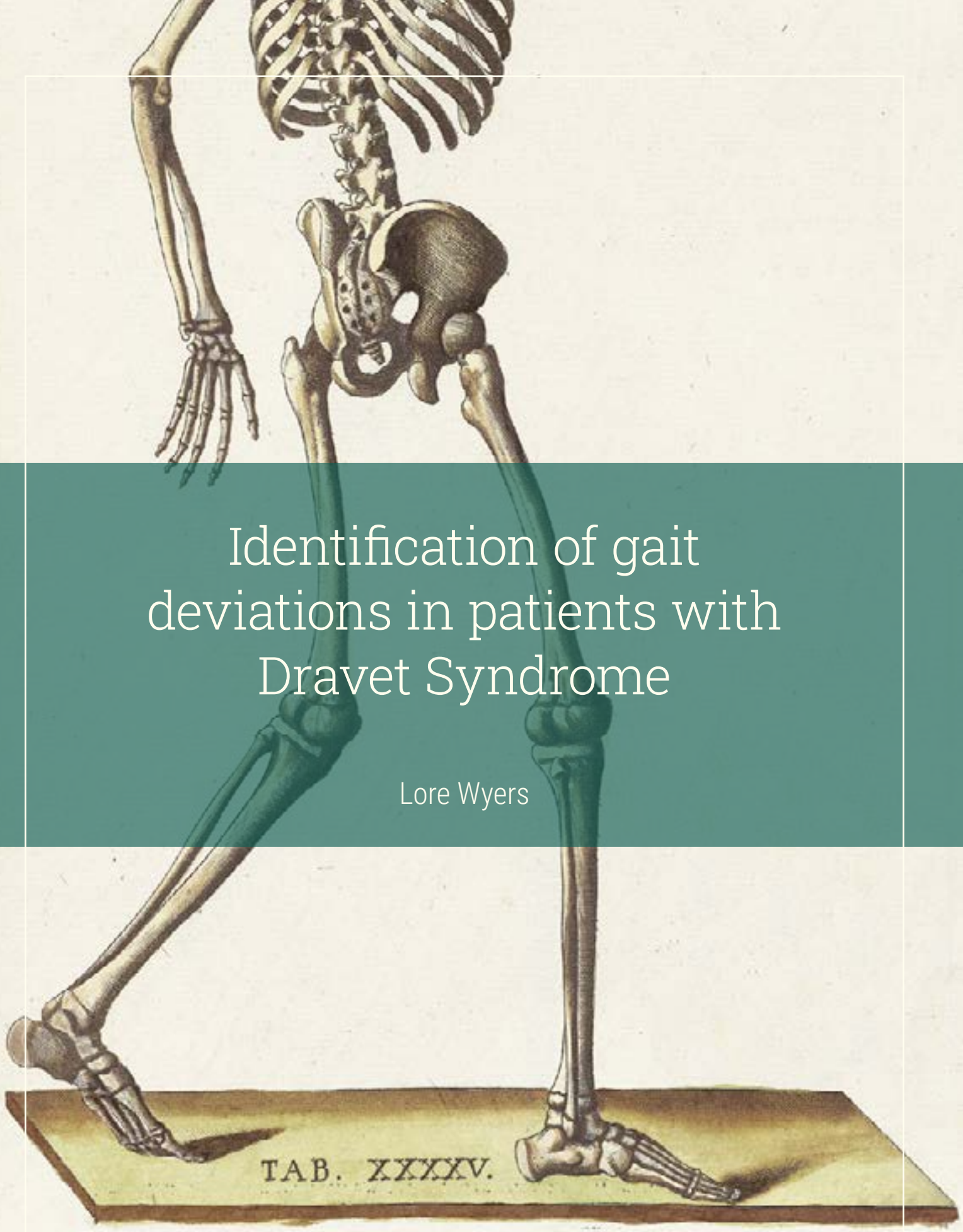

Identification of gait deviations in patients with Dravet Syndrome

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Identification of gait deviations in patients with Dravet Syndrome

Identificatie van gangafwijkingen bij patiënten met het Dravetsyndroom

Dissertation presented in partial fulfilment of the requirements for the joint degree of doctor of medical sciences (University of Antwerp) and doctor of biomedical sciences (KU Leuven)

by

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Table of content

Abbreviations

3DGA	Three Dimensional Gait Analysis
AFO	Ankle Foot Orthosis
CoP	Centre of Pressure
CoPP	Centre of Pressure Progression
DS	Dravet Syndrome
EMG	Elektromyography
EVGS	Edinburgh Visual Gait Score
FMS	Functional Mobility Scale
FSM	Functional Strength Measurement
GC	Gait Cycle
GRF	Ground Reaction Force
HGS	Hand Grip Strength
HHD	Handheld Dynamometry
IC	Initial Contact
ICF	International Classification of Functioning, Disability and Health
ID	Intellectual Disability
IGA	Instrumented Gait Analysis
ISw	Initial Swing
KMext	Subgroup defined by a persistint internal knee extension moment throughout stance regardless of trunk position
KMflex-Tf	Subgroup defined by an internal knee flexion moment in midstance in combination with forward trunk lean
KMflex-Tn/b	Subgroup defined by an internal knee flexion moment in combination with a neutral or backward inclined trunk

LR	Loading Response
MMT	Manual Muscle Testing
MS	Support Moment
MSt	Midstance
MVIC	Maximum Voluntary Isometric Contraction
Nav1.1	Sodium Channel Alpha-1 Subunit
PSw	Preswing
RoM	Range of Motion
SC	Stair Climbing
SCN1A	Sodium Voltage-Gated Channel Alpha-1 Subunit encoding gene
SD	Standard Deviation
SLJ	Standing Long Jump
SMEI	Severe Myoclonic Epilepsy of Infancy
SPARC	Spectral Arc Length
SPM	Statistical Parametric Mapping
STS	Sit To Stand
TCT	Total Contact Time
TD	Typical Development
T-GaiD	Treatment of Gait disorders in Dravet Syndrome (FWO-TBM project)
TO	Toe-off
TSt	Terminal Stance
UT	Underarm Throwing
VGA	Video Gait Analysis

Samenvatting

Patiënten met het Dravetsyndroom (DS) krijgen vaak te maken met moeilijkheden bij het gaan. Die gangproblemen vormen een beperking in het dagelijks leven en horen als comorbiditeit tot het brede ziektebeeld bij dit syndroom. Om inzicht te verwerven in de pathologische processen achter die problemen, is het nodig het gangpatroon te bestuderen. Wetenschappelijk onderzoek naar het gangpatroon bij patiënten met DS is echter nog zeer beperkt voorhanden, waardoor klinische adviezen voor de evaluatie en behandeling van gangproblemen onvoldoende gericht geformuleerd kunnen worden.

Voor dit doctoraatsproject werd als algemeen doel vooropgesteld om de belangrijkste afwijkingen in het gangpatroon bij patiënten met DS te karakteriseren. Twee literatuurstudies geven eerst een stand van zaken wat betreft bewegingsanalyse en gangafwijkingen bij patiënten met verstandelijke beperkingen in het algemeen en DS in het bijzonder. Vervolgens worden de biomechanische aspecten van de gang bij kinderen, adolescenten en volwassenen gedocumenteerd op basis van empirisch onderzoek.

Hoofdstuk 1 beschrijft een systematische literatuurstudie over gangafwijkingen bij populaties met verstandelijke beperkingen, bespreekt het standaard ganganalyseprotocol met zijn voordelen en uitdagingen, en presenteert een casusrapport van een patiënt met DS. In *hoofdstuk 2* komt eveneens een systematische literatuurstudie aan bod, ditmaal naar het gangpatroon bij patiënten met DS. *Hoofdstuk 3* vergelijkt 3D-ganganalysegegevens van deelnemers met DS met die van typisch ontwikkelende leeftijdsgenoten. Daarenboven worden strategieën gedetecteerd die het onderste lidmaat stabiliseren tijdens de steunfase. De bijhorende afwijkingen in kinematica, kinetica en het klinisch beeld worden gekarakteriseerd. Vervolgens beschrijft *hoofdstuk 4* de voetfunctie aan de hand van voetdrukmetingen tijdens het gaan patiënten met DS in vergelijking met typisch ontwikkelende leeftijdsgenoten. Tot slot wordt in *hoofdstuk 5* de haalbaarheid van spierkrachtmetingen bij patiënten met DS onderzocht.

In de literatuur werd het gangpatroon zowel bij patiënten met DS als bij de algemene populatie met verstandelijke beperkingen vaak beschreven als een ‘crouch’ (hurkend) patroon. De resultaten van het huidige onderzoek bevestigden dat vermeerderde knieflexie de momentwerking rond de grote gewrichten van het steunbeen benadeelde, wat het gangpatroon minder efficiënt maakt. Op basis van het extensormoment rond de knie en rompbewegingen werden drie kinetische strategieën geïdentificeerd die het steunbeen

stabiliseren. Bovendien bleek de voetfunctie verstoord, aangezien de helft van de deelnemers niet steevast met de hiel eerst de grond raakte en afwijkingen vertoonde in de drukverplaatsing onder de voet tijdens de steunfase. Hoewel de haalbaarheid van krachtmetingen bij deze populatie laag bleek, werden aanwijzingen voor verminderde spierkracht waargenomen.

Een inefficiënt gangpatroon werd geïdentificeerd, hoofdzakelijk gekenmerkt door vermeerderde flexie in de knie en een verscheidenheid aan neurologische, motorische en musculoskeletale afwijkingen. Om de waargenomen gangafwijkingen bij patiënten met DS begrijpen worden twee centrale hypothesen opgesteld. Ten eerste suggereert de *musculoskeletale hypothese* dat hefboomarmdysfunctie van de voet en verminderde spierkracht slechts gedeeltelijk de gangafwijkingen kunnen verklaren. Ten tweede stelt de *motorische controlehypothese* dat verstoorde neuromotorische controle en vertraagde psychomotorische ontwikkeling een niet te onderschatten rol spelen bij het ontstaan van gangafwijkingen bij patiënten met DS.

Summary

Patients with Dravet syndrome (DS) are often confronted with walking problems. As a comorbidity in the broad clinical picture of this syndrome, walking problems form a disabling factor. Studying gait deviations provides insight into the pathological processes that underlie walking problems. Research on gait in patients with DS is, however, still limited. This makes it difficult to formulate clinical advice for the evaluation and treatment of walking problems

This PhD project aimed to characterise the main gait deviations in patients with DS. First, the state-of-the-art regarding motion analysis and gait deviations in patients with intellectual disabilities (ID) and DS is established. To this end, two review studies are conducted. Thereafter, three empirical studies document biomechanical aspects of gait in children, adolescents and young adults with DS.

Chapter 1 provides an update of a systematic review regarding gait in populations with ID, a discussion of the standard gait analysis protocol with its benefits and challenges, and a case report of a patient with DS. *Chapter 2* also reports a systematic literature review, this time concerning gait in patients with DS. In *chapter 3*, a case-control study compares 3D gait analysis data of participants with DS with typically developing peers. In addition, lower limb support strategies and their characteristic deviations in kinematics and kinetics are identified. Thereafter, *chapter 4* investigates foot function in patients with DS compared to typically developing peers using pedobarography. And lastly *chapter 5*, documented the feasibility and validity of strength assessments in patients with DS and outlined strength problems.

Literature often described gait deviations as crouch gait in patients with DS as well as in the general population with ID. The results of the current research project confirmed that increased knee flexion increased the lower limb support moment in stance, reducing the efficiency of the gait pattern. Based on knee extensor moments and trunk lean, three kinetic strategies to maintain stance limb stability were identified. Moreover, foot function seemed impaired, as half of the participants did not consistently perform heel strikes and showed deviations in plantar pressure measures. Even though feasibility of strength measurements was low in this population, indications of decreased muscle strength were observed.

An overall inefficient gait pattern was identified, mainly characterised by increased knee flexion and diverse neurologic, motor and musculoskeletal deviations. Two main hypotheses

are formulated to explain the observed gait deviations in patients with DS. First, the *musculoskeletal hypothesis* suggests that in DS, decreased muscle strength and lever arm dysfunction only partly explain the gait deviations. Second, the *motor control hypothesis* states that the contribution of impaired neuromotor control and delayed psychomotor development to gait deviations in patients with DS should not be underestimated.

Introduction

Introduction

1. Background

Patients with Dravet Syndrome (DS) are often confronted with walking problems. As a comorbidity in the broad clinical picture of this syndrome, walking problems are a disabling factor. Walking is a crucial activity in everyday life, as it is our main way to move around. In the absence of pathology, walking is effortless and efficient and can easily be performed for several kilometres. But impairments can disturb a person's walking capacities and consequently affect many aspects of daily functioning. In the international classification of functioning, disability and health (ICF, Figure 1), walking is situated on the level of activities, as part of mobility (World Health Organization 2001). Walking problems affect activities that involve walking relatively short distances inside, but also walking longer distances outside, running, climbing stairs, avoiding obstacles, etc. Moreover, they interfere with one's social and community life, for example by restricting participation in sports or school trips. While walking performance in a daily context is situated on the activity level, the manner of walking in a standardized environment or the 'gait pattern' is situated on the body function level. On the level of body functions and structures, several impairments are known to interact with gait. More specifically, impairments of the lower extremity structures, of joint and muscle function and of neuromotor control can result in an impaired gait pattern. The analysis of gait deviations is therefore an important component in elucidating the pathological processes underlying walking problems.

In order to improve the daily functioning of patients with DS, interventions addressing gait may be desirable. However, the nature of walking problems in patients with DS remains unclear, resulting in a lack of knowledge that is essential to select appropriate interventions. To fill this gap, the FWO-TBM project "T-GaiD: Treatment of Gait disorders in Dravet syndrome" started in 2017 as a collaboration between the University of Antwerp, the Antwerp University Hospital, the KU Leuven and the University Hospitals Leuven. The project emerged from a large follow-up study on development in DS ("Het Pad van Dravet") at the Antwerp University Hospital (Ceulemans 2011). The main goal of the T-GaiD project was to develop a clinical decision making framework for the follow-up and treatment of gait disorders. The current PhD project is situated within the T-GaiD project and investigates the characteristics of gait deviations in patients with DS.

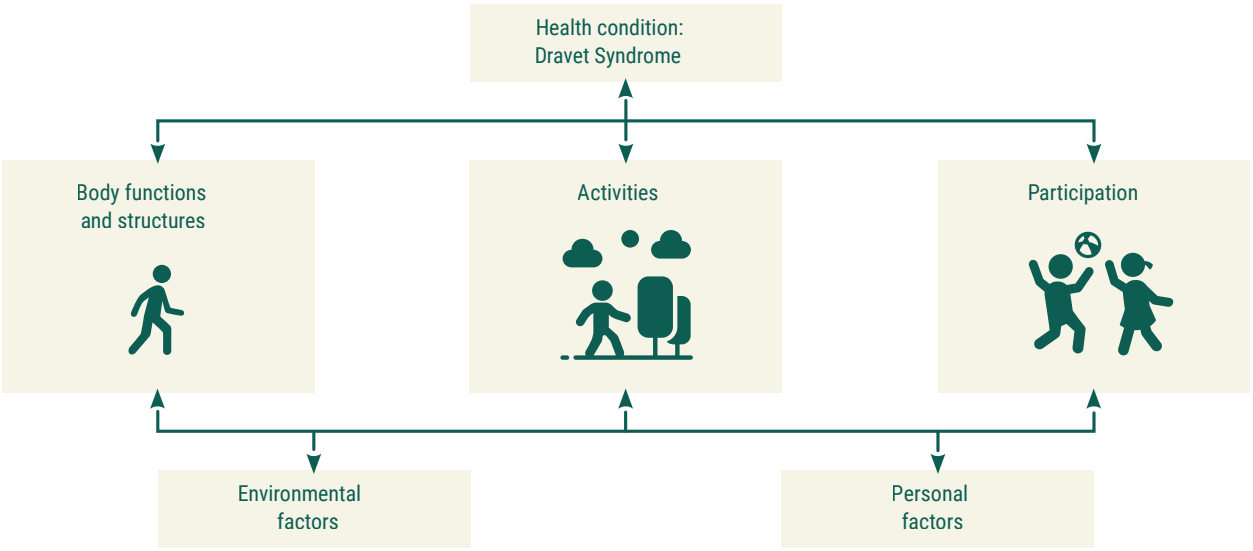

Figure 1. Walking problems are a comorbidity in the broad clinical picture of Dravet Syndrome. In the international classification of functioning, disability and health (ICF), walking problems are situated on the level of activities. Gait deviations are situated on the level of body functions.

This introduction starts with a general description of DS with an emphasis on walking problems. Further, the basic principles of gait analysis are discussed. Subsequently, an overview of the aims, an outline and the methods of this dissertation are presented.

1.1 Dravet Syndrome

1.1.1 Definition and pathophysiology

DS is a severe childhood onset epilepsy syndrome with impaired cognitive and motor development. Its incidence is estimated between 1/15.000 and 1/40.000 (Wu et al. 2015; Brunklaus et al. 2012). The syndrome was first described by Charlotte Dravet in 1978 and previously called "Severe Myoclonic Epilepsy of Infancy (SMEI)" (Dravet 1978). It is classified as a developmental and epileptic encephalopathy, which indicates that the developmental delay and epileptic activity are secondary to an underlying genetic mutation (Scheffer et al. 2017; Nabbout et al. 2013).

More than 80% of patients with DS have mutations in *SCN1A*, the gene encoding the sodium channel alpha-1 subunit (Nav1.1) (Claes et al. 2001; Depienne et al. 2009; Scheffer and Nabbout 2019). Most of these mutations occur de novo. The Nav1.1 proteins transport action potentials over cell membranes and are primarily expressed in interneurons of the central nervous system. Mouse models show that loss of function mutations in Nav1.1 cause epilepsy, as well as co-morbidities such as ataxia, sleep impairment, cognitive deficits and autistic-like behaviour (Catterall 2018). These findings point towards a 'channelopathy'

or ‘interneuronopathy’ model where co-morbidities are not purely consequences of epileptic seizures (Kalume et al. 2007; Brunklaus and Zuberi 2014).

1.1.2 Clinical picture

Epilepsy in DS has a characteristic profile in terms of age of onset, evolution of seizure types and electroencephalographic features (Dravet 2011; Scheffer 2012). DS typically presents itself in the first year of life with febrile seizures, usually a clonic or tonic-clonic convulsion. During childhood, additional seizure types appear and over time, seizures might become less triggered by fever and frequently occur during sleep (Dravet 2011; Ceulemans and Cras 2004; Scheffer and Nabbout 2019). Slight temperature variations, physical exercise, emotions and other stimuli can trigger seizures and photo- and pattern sensitivity are frequent (Dravet 2011). Epilepsy in DS is typically drug-resistant, although in recent years promising new pharmacological treatments have been developed (Cross et al. 2019). More specifically, the repurposed fenfluramine, previously used as an appetite suppressant, proved to be effective in controlling seizures in patients with DS (Lagae et al. 2019; Schoonjans et al. 2017).

Cognitive and behavioural deficits are common in patients with DS (Battaglia et al. 2016; Dravet 2011). Early psychomotor development appears normal, but slowing and stagnation occur, leading to a marked developmental delay after the age of two (Wolff, Cassé-Perrot, and Dravet 2006; Ceulemans and Cras 2004; Battaglia et al. 2016). A range from low average intelligence to profound intellectual disability (ID) is observed, mostly moderate and severe ID (Brown et al. 2020; de Lange et al. 2019). Commonly reported behavioural problems in DS are hyperactivity, attentional deficits, recalcitrant behaviour and atypicality (Wolff, Cassé-Perrot, and Dravet 2006; Brown et al. 2020; Sinoo et al. 2019; de Lange et al. 2019).

Motor development is delayed, which is often already noticeable before the age of two. Gross motor milestones such as sitting and walking independently, are achieved late in about half of the population. After the age of two, all patients show a delay in gross and fine motor development (Wolff, Cassé-Perrot, and Dravet 2006; Verheyen, Verbecque, et al. 2019). This delay seems to increase and reach a plateau, mainly in gross motor development (Verheyen, Verbecque, et al. 2019; Ceulemans 2011).

Walking problems are frequently reported in patients with DS. Unstable gait or ‘clumsiness’ after the onset of independent walking may take longer to dissolve (Scheffer 2012). Walking difficulties increase with age and become a major concern before adolescence (Rodda et al. 2012; Lagae et al. 2018; Camfield, Camfield, and Nolan 2016). A progressive crouch gait

pattern is described in children and adolescents with DS (Rodda et al. 2012). Patients usually maintain the ability to walk around the house, but loss of mobility for longer distances is frequently reported with wheelchair use in 20% to 40% of the patients (Baker et al. 2012; Lagae et al. 2018; de Lange et al. 2019). Parents and caregivers indicate that walking problems, among other comorbidities, strongly affect the quality of life of patients and their families (Villas, Meskis, and Goodliffe 2017; Knupp et al. 2017; de Lange et al. 2019; Lagae et al. 2018).

1.1.3 Evaluation and treatment

The main focus in the management of patients with DS is evidently on seizure control. Recently however, increasing attention is being paid to comorbidities, including walking problems (Ceulemans 2011; Ziobro et al. 2018; Lagae et al. 2018). There is strong consensus that screening for gait disorders should be routinely performed, starting in early childhood and that, in case of gait deviations, referral to physiotherapy should be made (Wirrell et al. 2017). In 2019, this insight was converted into a guideline ("Richtlijn Dravetsyndroom") established by the Vereniging Klinische Genetica Nederland (VKGN). The guideline included a chapter on gait ("Monitoring lopen bij Dravetsyndroom") with four main recommendations: (1) referral to a rehabilitation physician after the onset of independent walking to discuss an exercise program and, if necessary, a consultation with an orthopaedic surgeon, (2) prescription of valgus corrective devices (insoles or supramalleolar orthoses) at the onset of independent walking in case of planovalgus feet and hypotonia, (3) consideration of physiotherapy for specific strength training of leg and trunk musculature and stimulation of motor development and (4) raising awareness of parents to continuously activate motor skills by practicing activities of daily living. Furthermore, the guideline advised annual monitoring of mobility and gait, with the consideration of instrumented gait analysis (Vereniging Klinische Genetica Nederland 2019).

Although the guideline recognised the need to monitor gait and early interventions, it could not provide more details on when and how gait analysis should be applied and how it can support the four recommendations of the guideline. Research on gait in patients with DS is lacking, which impedes the documentation of the specific needs in this population. Numerous studies support the importance of gait analysis to identify the causal factors behind observed deviations and to improve treatment selection. However, the vast majority of this research is performed in populations with cerebral palsy (Gage 1993; Whittle 1996; Baker et al. 2016; Armand, Decoulon, and Bonnefoy-Mazure 2016; Wren et al. 2011). Nevertheless, growing

evidence shows that the use of gait analysis can be extended to other populations (Baker et al. 2016; Almuhtaseb, Oppewal, and Hilgenkamp 2014). To enable transfer of this knowledge and experience to patients with DS, studies on gait in this population are needed.

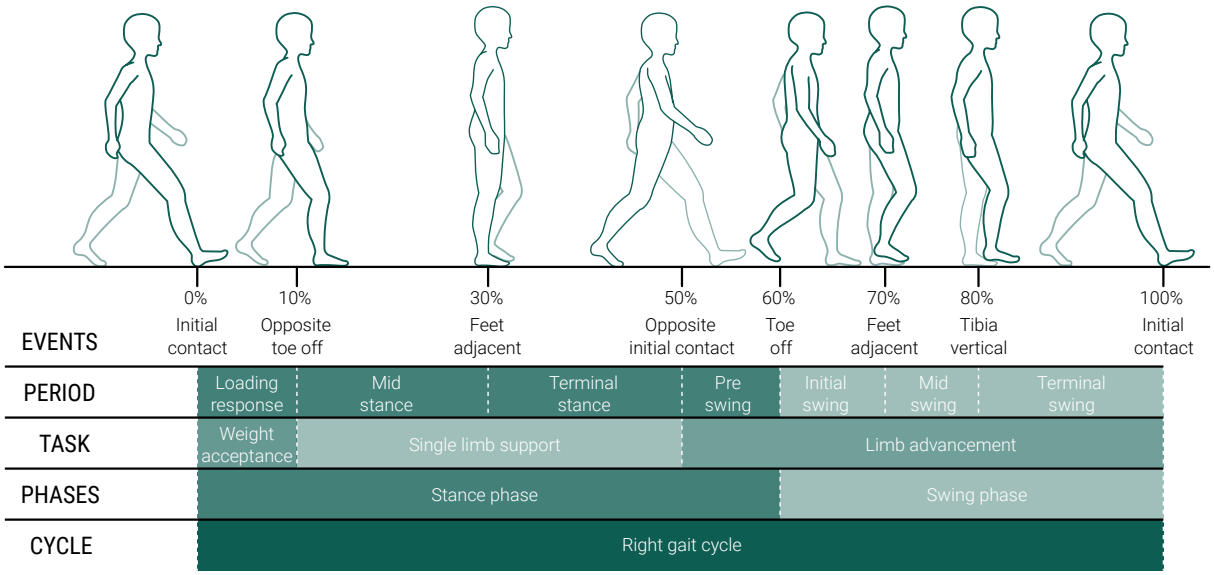

Figure 2: The gait cycle is subdivided into functional phases.

1.2 Gait

1.2.1 Basic concepts

Gait is defined by the use of repetitive limb motion to move the body around. While one limb is in contact with the ground and provides stability, the other limb moves forward and prepares itself to become the supporting limb. It is a complex task that requires smooth interaction of numerous muscles; yet it is highly automated, which allows us, for example, to avoid obstacles and adapt to different surfaces while talking on the phone. Walking forward on a level surface is the fundamental pattern of human gait (Perry and Burnfield 2010). Impairments of lower extremity structures, joint and muscle function and neuromotor control may disturb the normal gait pattern. Studying gait deviations therefore provides insight into the integrity of the musculoskeletal and neuromotor control systems (Winter 1983; Baker et al. 2016).

Gait is usually approached by considering one gait cycle (GC) starting from the moment one foot strikes the ground (initial contact) until the subsequent strike of the same foot on the ground (Figure 2). The GC consists of a stance phase and a swing phase and can be further subdivided into smaller periods, each of which fulfils a functional task (Perry and Burnfield 2010; Baker 2013). Gait analysis investigates whether these tasks are successfully and efficiently performed.

1.2.2 Gait analysis

Gait pattern cans be described using qualitative, subjective observation augmented by quantitative, objective measurements of various aspects of the gait pattern. *Spatiotemporal parameters* describe the time and distance related aspects of gait, such as walking velocity, step length or stance phase duration. *Kinematics* concern the position and motion of body segments and joint angles throughout the gait cycle. *Kinetics* describe the forces that cause this motion, combining internal forces from muscles and soft tissue with external forces, primarily gravity. *Muscle activation patterns* reveal when the different muscle groups are activated during the gait cycle. *Plantar pressure* characterises the distribution of forces under the plantar surface of the foot throughout stance phase. During gait analysis, these features are recorded and interpreted in order to detect deviations from normal gait and identify possible causes. More details on the instruments and methods of gait analysis are presented in chapter 1 of this dissertation.

1.2.3 Biomechanics of gait

Biomechanics is the research field that applies mechanical principles to living organisms, in this case the human body. Understanding biomechanical principles is necessary for thorough interpretation of gait analysis results (Winter 1983). The motion of the body during gait is the result of internal and external forces that occur around the joints. The major external force involved in gait is the ground reaction force (GRF), the force provided by the supporting horizontal surface. The GRF is counteracted by internal forces from muscles and soft tissue. These forces produce moments around the joints and hence evoke motion. Many combinations of muscle forces can yield the same moment and many combinations of hip, knee and ankle moments can result in the same knee angle. Therefore, an integrated analysis of kinematics and kinetics should be performed to understand the mechanics, muscle function and thus neuromotor control behind gait (Winter and Eng 1995).

Gait is a dynamic situation during which *stability of the stance limb* should be maintained, while forward movement of the body is generated. Hereto, the GRF vector is continuously realigned relative to the lower limb joints during gait (Perry and Burnfield 2010). For example, ankle plantar flexors are active in midstance to slow down the forward progression of the tibia. As such, the GRF vector shifts anterior to the knee, stabilising the knee in extension during midstance (figure 3). This way, stability is passively maintained through soft tissue, such as ligaments, rather than through active knee extensor work. Normal gait is characterised by such *kinetic strategies* that optimise the energy expenditure (Perry and Burnfield 2010).

In the presence of pathology, a person may fail to attain optimal alignment. As a result, the required muscle work and thus energy demands increase (Gage 1993). Patients may develop alternative kinetic strategies to maintain stability, for example by forward trunk lean, which brings the GRF vector forward. Kinetic strategies of patients serve as a mirror to study their neuromotor control (Winter and Eng 1995). For this reason, we performed a study on the kinetic strategies in patients with DS, which is presented in chapter 3.

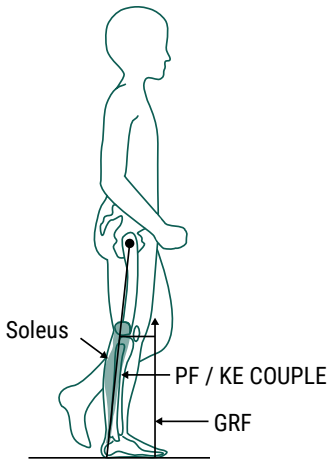

Figure 3. The plantar flexion-knee extension (PF/KE) couple. The plantar flexors control the forward displacement of the tibia during midstance and align the ground reaction force (GRF) vector anterior to the knee (Gage 1993).

The starting point for observing gait often focuses on the changing *pattern of foot contact* with the floor (Perry and Burnfield 2010). As the foot stays in contact with the ground during stance phase, it forms the first segment in the chain on which the GRF acts. The foot support pattern therefore reflects how the gait pattern is established starting distally. The normal gait cycle begins with the heel contacting the floor to accept the weight. It is immediately followed by foot flat contact in midstance to form a stable base of support. The stance phase ends with forefoot contact during terminal stance and pre swing to generate forward propulsion for the swing phase. Along with this contact pattern, the base of the GRF vector advances from the heel to the toes, passing from posterior to anterior from the ankle joint. Motor control deficits and structural or functional deformities of the foot, especially pes planovalgus, are present in the population with DS. Such deficits can disturb this pattern with an immediate impact on moments around the ankle joint and consequently on the entire gait pattern. Therefore, chapter 4 will investigate the foot contact patterns in patients with DS.

In addition to efficient neuromotor control, a well-functioning *musculoskeletal system* is also required for normal gait. Adequate muscle length and joint range of motion is necessary to

extend the stance limb and flex the swinging limb. Furthermore, good anatomical alignment is needed for body segments to serve as lever arms to enable optimal muscle function.

Finally, sufficient *muscle strength* is a prerequisite for stabilising and moving the body against gravity (Brunner and Rutz 2013). Structural and functional impairments of bones, joints and muscles result in gait deficits. Therefore, physical examination is usually part of gait analysis to improve clinical interpretation of the results (Baker et al. 2016; Desloovere et al. 2006). In patients with DS, musculoskeletal impairments may occur as cause or consequence of gait deviations. Foot deformities and malrotation of bones, such as planovalgus feet and external tibial torsion have previously been described in patients with DS (Rodda et al. 2012). It remains, however, unclear whether muscle strength may be impaired. Since muscle weakness is a major contributor to gait deviations, especially crouch gait (van der Krogt, Delp, and Schwartz 2012; Brunner and Rutz 2013), chapter 5 presents a study on muscle strength in patients with DS.

2. Aims and outline

The overall aim of this PhD project was to characterise the main gait deviations in patients with DS. The objective in part I of this dissertation was to establish the state-of-the-art regarding motion analysis and gait deviations in patients with ID and DS. To this end, two review studies were conducted. In part II, the objective was to document biomechanical aspects of gait in children, adolescents and young adults with DS. For this purpose, three empirical studies were realised. Altogether, these five studies form the main chapters of this dissertation, followed by a general discussion (Figure 4).

Figure 4. Outline of the dissertation. ID, Intellectual Disabilities; DS, Dravet Syndrome

2.1 Part I: State-of-the-art

Chapter 1: Clinical usefulness and challenges of instrumented motion analysis in patients with intellectual disabilities

This narrative review aims to establish an overview of gait features that are common in a population with intellectual disabilities (ID) as well as to discuss potential benefits and challenges of performing instrumented motion analysis in patients with ID. The review consists of three main parts. First, an update of a systematic review concerning gait in populations with ID is performed. Second, the standard gait analysis protocol with its benefits and challenges is discussed. Lastly, a case report of a patient with DS is presented.

Chapter 2: Gait deviations in patients with DS: a systematic review

This study aims to provide an overview of the current research on evaluation of gait in

patients with DS. A systematic literature review is performed by consulting four databases to select all studies evaluating gait in patients with DS. Outcomes related to gait on levels of body structure, function, activities and participation are discussed.

2.2 Part II: Biomechanical aspects

Chapter 3: The mechanics behind gait problems

This study aims to characterise the kinetic strategies in gait of patients with DS to support the lower limb during the stance phase. A case-control study compared 3DGA data of participants with DS with typically developing (TD) peers. Lower limb support strategies and their characteristic deviations in kinematics and kinetics is described.

Chapter 4: Foot-floor contact patterns

This study aims to investigate foot function in patients with DS by characterising foot-floor contact patterns. In this case-control study, pedobarography is used to document foot strikes and plantar pressure during gait in a group of patients with DS compared to TD peers.

Chapter 5: Strength measurements

This study aims to determine how feasible and valid strength measurements are in the framework of gait analysis in patients with DS and to outline strength problems in patients with DS. In a cross-sectional study, strength assessments are performed in patients with DS. Completion rate, challenges and implications of the measurement outcome is discussed.

This dissertation concludes with a general discussion to synthetize the five chapters and discuss their clinical implications and directions of future research.

Chapter 1

Clinical usefulness and challenges of instrumented motion analysis in patients with intellectual disabilities

Chapter 1

Clinical usefulness and challenges of instrumented motion analysis in patients with intellectual disabilities

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1. Abstract

Background: Clinical laboratory testing of locomotor disorders is challenging in patients with intellectual disability (ID). Nevertheless, also in this population gait analysis has substantial value as motor problems are common. To promote its use, adequate protocols need to be developed and the impact on clinical decision making needs to be documented.

Research question: What is the clinical usefulness of instrumented motion analysis in patients with ID?

Method: This narrative review consists of three parts. A literature review was performed to describe the gait pattern of patients with ID. Next, benefits and challenges of standard gait analysis protocols are described. Finally, a case of a girl with ID due to genetic cause showing gait abnormalities is discussed.

Results: The literature review resulted in 20 studies on "gait" in patients with an "ID", published since August, 1st 2013. Gait deviations were observed in all studies investigating the ID population with an underlying genetic syndrome. Observed gait deviations in the ID population might be attributed to physical characteristics, cognitive components or both. The main goal of clinical gait assessment is the identification of gait deviations and the evaluation of their progress over time, in order to optimize the treatment plan. The choice of adequate method and measurement modalities depends on the clinical goal, the available resources and the abilities of the patient. In the case report we presented, we succeeded in performing an instrumented 3D gait analysis in a girl with severe ID at the ages of 4y4m, 6y0m, 7y2m and 8y2m. Progressive gait deviations were found suggesting a crouch gait pattern was developing. Results of the gait analysis led to the prescription of rigid ankle-foot orthoses.

Significance: Gait analysis has substantial value for patients with ID. Gait analysis allows clinicians to objectify the relationship between physical characteristics and gait features.

2. Introduction

Gait analysis, when combined with physical examination, provides quantitative information to guide treatment of gait disorders and assess its outcome. Since the 1990s gait analysis has become standard procedure in the treatment of gait problems in children with cerebral palsy (Gage, Deluca, and Renshaw 1995). Gait analysis affords the confidence not provided

by clinical examination that the correct number and selection of treatment procedures can be chosen (Baker et al. 2016; Desloovere et al. 2006). Despite the value of gait analysis, clinical laboratory testing of locomotor disorders is not yet wide spread in other populations than children with cerebral palsy or post-stroke patients. The issue of use does not relate to its perceived value but to the challenges faced by the gait analysis protocol (McGinley et al. 2009). Especially in patients with intellectual disability (ID), difficulties in understanding instructions and lack of body awareness during physical examination could negatively affect the result of the gait analysis.

Nevertheless, gait analysis has substantial value for patients with ID. Gait is a highly relevant functional motor skill. In the older adult population, poor gait performance is linked to co-morbidity, risk of falling (Callisaya et al. 2010), disability and mortality (Ambrose, Paul, and Hausdorff 2013). Given that people with ID already experience lifelong levels of low physical activity (A Oppewal et al. 2014; 2015), identifying and treating possible gait abnormalities to keep them active as long as possible is of utmost importance.

ID might originate from a range of different causes being either genetic (e.g. Down Syndrome, Prader-Willi syndrome, Williams syndrome) or acquired (e.g. cerebral palsy, herpes encephalitis, lead intoxication). Delayed motor development is often seen in the population with ID, certainly at a younger age. A delayed onset of walking, after the age of 16 months, is common and occurs in 1 out of 5 children with ID (Bishop et al. 2016). Children with borderline intellectual function and mild ID score below the norm on motor function tests (Hartman et al. 2010; Houwen et al. 2016; Smits-Engelsman and Hill 2012; Vuijk et al. 2010). Children with more severe ID show even poorer motor performance (Hartman et al. 2010; Smits-Engelsman and Hill 2012; Vuijk et al. 2010). Both in typically developing (TD) and ID populations, significant correlations have been found between motor performance and cognitive functions such as IQ, executive function and language development (Kim et al. 2016; Houwen et al. 2016; Smits-Engelsman and Hill 2012) with stronger relations between developmental domains in ID (Houwen et al. 2016). In populations with mild and borderline ID, 19 to 23% of the variance in motor functions can be explained by cognition (Hartman et al. 2010). The neuroanatomical theory of common pathways explaining the coupling between motor function and cognition is supported by both behavioral research and central imaging (Dockstader et al. 2012; Spann et al. 2014). Motor control and cognition share common pathways in the dorsolateral prefrontal cortex, cerebellum and connecting structures including the basal ganglia (Hartman et al. 2010; Houwen et al. 2016). The strong coupling between the different developmental domains in the ID population might thus be

related to a higher incidence of brain anomalies and an atypical function of the brain (i.e. atypical brain development concept of Kaplan) (Houwen et al. 2016; Vuijk et al. 2010).

The role of cognition in gait has to be recognized. Cognitive functions such as integration of attention, planning, memory and perception all play an important role (Verlinden et al. 2014). As such, gait abnormalities can be expected in individuals with ID. Nevertheless, several patients with ID, especially with underlying genetic cause, also show physical abnormalities that might affect their gait pattern. In order to treat potential gait abnormalities in patients with ID, a better understanding of the contribution of physical features and cognitive components is necessary. In 2014, Almuhtaseb and co-workers (Almuhtaseb, Oppewal, and Hilgenkamp 2014) performed a systematic literature review on gait characteristics in individuals with ID. They showed that gait abnormalities are evident in the ID population, both in people with genetic syndromes and with acquired ID. Physical characteristics, such as hypermobility, ligament laxity and muscle hypotonia in Down syndrome or severe obesity in Prader-Willi syndrome had a considerable biomechanical effect on the gait pattern. However, the specific physical features do not explain all of the gait abnormalities in the ID population. To better understand this, the relation between gait and cognition deserves attention.

The overall aim of this narrative review is to provide the reader with an overview of the gait features that are common in a population with ID as well as discuss potential benefits and challenges of performing instrumented gait analysis in patients with ID. As such this review consists of three main parts. First we will provide an update of the literature (Almuhtaseb, Oppewal, and Hilgenkamp 2014) to identify gait abnormalities common in populations with ID and formulate a hypothesis on the link between cognition and gait; second we will discuss the standard gait analysis protocol with its benefits and challenges; third we will present a case report of gait abnormalities in a patient with severe ID due to a genetic cause (syndrome of Dravet) and link this to information from literature.

3. Central body

3.1 Gait abnormalities in patients with an intellectual disability

An update of the systematic review by Almuhtaseb (Almuhtaseb, Oppewal, and Hilgenkamp 2014) was performed using the same search strategy. The search query [(intellectual disability) AND gait] was entered in Pubmed on May 3rd, 2018 and publication date limits were set starting from August 1st, 2013 (table1). Two researchers (A.H. and L.W.) independently screened the citations on title and abstract according to predetermined criteria. The screening

results were discussed until consensus was found and selected articles were subjected to screening on full text using the same criteria. Articles were included when the population (P) consisted of participants with ID of any age, when the primary outcome (O) described gait characteristics in terms of spatio-temporal parameters, kinematics, kinetics and/or dynamic electromyography collected during overground and unperturbed locomotion (I) and when the study (S) contained original research published in English, Dutch, French or German. Occasional and subjective reports on gait deviations in merely genetical or pharmacological research and case reports were excluded. Two researchers (A.H. and L.W.) extracted the following data using a structured form: study characteristics (aim and design), population (diagnosis, inclusion and exclusion criteria and participant characteristics), measurement equipment and protocol, statistical analysis, outcome measures and results.

Table 1 Search Details

User Query	(intellectual disability) AND gait
Filter	Publication date: From 1/08/2013
Query Translation (Pubmed)	("intellectual disability"[MeSH Terms] OR ("intellectual"[All Fields] AND "disability"[All Fields]) OR "intellectual disability"[All Fields]) AND ("gait"[MeSH Terms] OR "gait"[All Fields]) AND ("2013/08/01"[PDAT] : "3000/12/31"[PDAT])

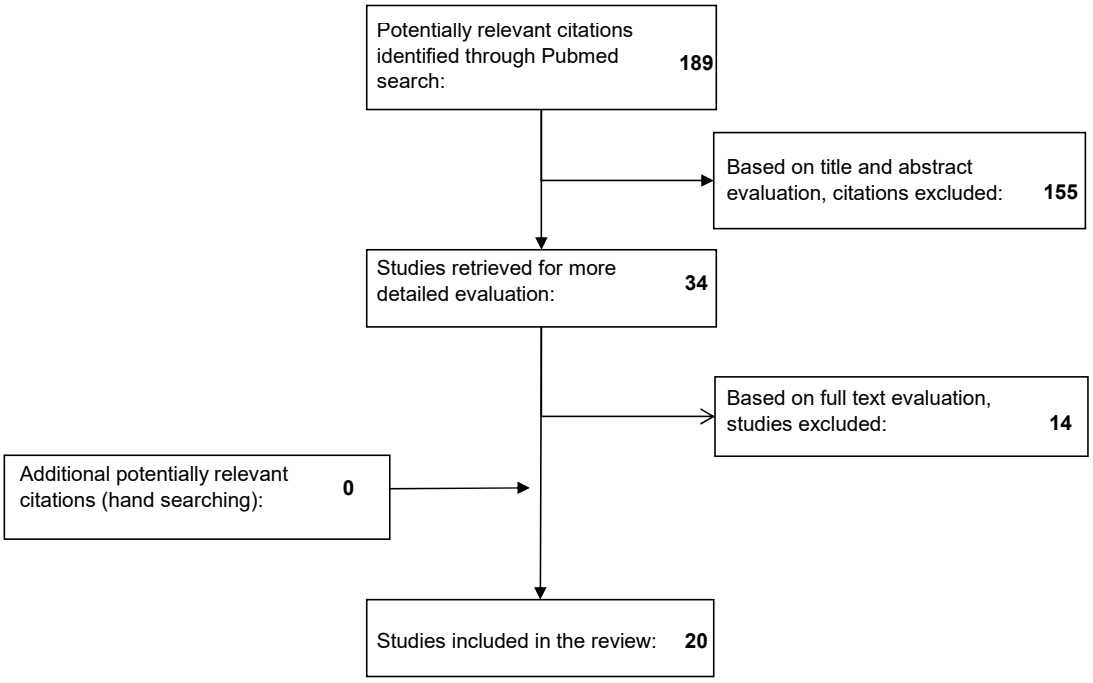

Figure 1. Flow diagram of the study selection process

Study	Design	Population	N	Age	ID level	Sex M/F	Walking condition	barefoot/ shoes	Aparatus or equipment for measuring gait + protocol	Outcome measures
Abbruzzese LD et al. 2016	Case-control	CDC 	28 14 CDC 14 CG	3-20 10.3 (5.7) 10.1 (5.4)	N/A	 2M/ 12F 4M/ 10F	overground at preferred speed	N/A	GaitRite instrumented walkway (4.6 m)	STP
Cazaletts et al. 2017	Case-control	RTS 	42 25 RT 18 CG	11-20 14.7 (3) 15.1 (2.5)	IQ range 30 - 99	 10M/15F 8M/ 10F	overground at preferred speed	N/A	3D video motion system (Elite BTS, 100 Hz.)	STP Gait Variability
Cimolin et al. 2014	Cohort	PWS 	32 8 PW 10 CG 14 O_CG	 28.7 (4.8) 33.4 (9.6) 29.4 (7.9)	mild ID (MMSE > 24)	 4M/ 4F 5M/ 5F 5M/ 9F	overground at preferred speed	barefoot	3D video motion system (Vicon Mcam 460), Plug-in Gait marker set-up	STP kinematics kinetics
Djukic et al. 2016	Cohort	RS 	10 RS	12-16	N/A	10F	overground at preferred speed	N/A	GaitRite instrumentend walkway (8.5 m)	STP
Galli et al. 2015	Case-control	DS 	98 40 O_DS 38 DS 20 CG	5-18 12.4 (2.8) 13.0 (3.1) 13.7 (3.5)	low to medium IQ	 21M/19F 18M/20F 10M/10F	overground at preferred speed	barefoot	3D video motion system (BTS Smart-D, 100 Hz.), Davis marker set-up	STP kinematics kinetics
Galli et al. 2014a	Case-control	DS 	44 29 DS 15 CG	 9.8 (2.3) 9.2 (5.7)	low to medium IQ	N/A	overground at preferred speed	barefoot	Idem Galli et al., 2015	kinetics
Galli et al. 2014b	Case-control	DS 	70 55 DS 15 CG	 9.6 (1.7) 9.2 (5.7)	low to medium IQ	N/A	overground at preferred speed	barefoot	Idem Galli et al., 2015	kinematics
Hocking et al. 2014	Case-control	 DS WS 	53 17 DS 18 WS 17 CG	 24.8 (3.0) 26.2 (7.3) 23.2 (6.1)	 	 8M/ 9F 7M/ 11F 11M/ 6F	overground at preferred speed	N/A	GaitRite instrumentend walkway (8.5 m)	STP STP Gait Variability
Horvat et al. 2013	Case-control	DS 	24 12 DS 12 CG	18 - 28 22.7 (3.1) 22.5 (3.12)	N/A	N/A	overground at preferred speed	N/A	GaitRite instrumentend walkway (6.96 m)	STP
Iosa et al. 2014	Case-control	 DS – ASD - PDD 	25 18 ID 7 CG	 17.2 (5.2) 10.3 (0.5)	mental age 7 - 11 years	 	overground at preferred speed	N/A	wearable intertial sensor (Freesense, Sensorize, Rome; 100 Hz.)	STP

Study	Design	Population	N	Age	ID level	Sex M/F	Walking condition	barefoot/ shoes	Aparatus or equipment for measuring gait + protocol	Outcome measures
Lee et al. 2016	RCT		31	16.68 (1.70)	IQ range	17M/ 14F	overground at	regular footwear	10 m walk test	STP
		DS	21 DS		50 - 70		preferred speed			
		US	10 US							
Lee et al. 2014	RCT		40		mild to	21M/ 19F	overground at	barefoot	GaitRite instrumentend walkway (5 m)	STP
		DS	27 DS		moderate ID		preferred speed			
		US	13 US							
Malatesta et al. 2013	Case-control	PWS	30		mild ID		overground at	barefoot	3D video motion system (Vicon)	STP
			15 PWS	26.7 (1.5)	(MMSE > 24)	7M/ 8F	preferred speed		Plug-in Gait marker set-up	
			15 O_CG	28.7 (1,9)		7M/ 8F				
O'Keefe et al. 2016	Case-control	FXTAS	31	60-80	N/A	11M /20F	overground at	N/A	six inertial sensor system (APDM), instrumented	STP
			7 FXTAS+	69.57 (4.89)		4M/ 3F	preferred speed		timed up and go (7m walk)	Gait Variability
			6 FXTAS -	65.33 (7.45)		1M/ 5F				
			18 CG	68.7 (5.1)		6M/ 12F				
Oppewal et al. 2017, 2018a, 2018b	cross-sectionalvt	ID	31	42.77 (16.70)	mild (IQ 50 - 69, n = 15), moderate (IQ 35 - 49, n = 16)	24M/ 7F	overground at preferred speed	N/A	GaitRite instrumentend walkway (5.79 m)	STP Gait Variability
Salami et al. 2014	Case-control	DS	39		35<IQ<70	N/A	overground at	N/A	3D video motion system (Elite BTS, 100 Hz.)	STP
			21 DS	21.6 (7)			preferred speed			
			18 CG	25.1 (2.4)						
Salb et al. 2017	cross-sectional	ID	32	59.6 (16.7)	18 mild/ moderate 14 severe/ profound	6M/ 26F	overground at preferred speed	barefoot	GaitRite instrumentend walkway (6.10 m)	STP
Shieh et al. 2016	Case-control	ID	52				overground	N/A	integrated sensor composed of three axis	STP
			20 ID	17.75 (0.97)	N/A	N/A			accelerometer and gyroscope (Xsens); 10m	
			32 CG	17.97 (1.60)	N/A	N/A			walk test	

Populations: ASD = Autism Spectrum Disorder, CDC = Cri du Chat syndrome, CG = control group, DS = Down syndrome, ID = intellectual disability, FXATS = Fragile X-associated tremor/ataxia syndrome, O_ = obese, PDD = Pervasive Developmental Disorder, PWS = Prader-Willi syndrome, RS = Rett syndrome, RTS = Rubinstein – Taybi syndrome, US = unknown syndrome, WS = Williams syndrome

Abbreviations: N = sample size, N/A = not available, M/F = male/female, STP = spatio-temporal parameters

Table 2
Characteristics of studies describing overground and unperturbed locomotion

The search yielded 189 articles that were published since August 1st, 2013. After screening on title and abstract, 155 articles were excluded. The remaining 34 articles were screened on full text and another 14 studies were excluded for not meeting the selection criteria. As such, 20 studies were included in this review, which can be considered an update of the literature review on gait characteristics in the ID population, published by Almuhtaseb (Almuhtaseb, Oppewal, and Hilgenkamp 2014) (Figure 1).

3.1.1 Descriptive information of the studies included

Twelve studies had a case-control design four were cross-sectional studies (Alyt Oppewal and Hilgenkamp 2017; Alyt Oppewal, Festen, and Hilgenkamp 2018; Alyt Oppewal and Hilgenkamp 2018; Salb et al. 2017) two were cohort studies (Cimolin et al. 2014; Djukic et al. 2016) and two were randomized controlled trials (K. Lee, Lee, and Song 2016; K. J. Lee et al. 2014).

Twelve studies investigated syndrome-specific ID populations, of which five were Down syndrome (DS) (Galli, Cimolin, Pau, et al. 2014; Galli et al. 2015; Galli, Cimolin, Rigoldi, et al. 2014; Hocking et al. 2014; Horvat et al. 2013; Salami et al. 2014), two were Prader – Willi syndrome (PWS) (Malatesta et al. 2013; Cimolin et al. 2014), one Cri du Chat syndrome (CDC) (Abbruzzese et al. 2016), one Fragile – X associated tremor/ataxia syndrome (FXAT+) (O'Keefe et al. 2014), one Rett syndrome (RS) (Djukic et al. 2016), one Rubinstein – Taybi syndrome (RTS) (Cazalets et al. 2017) and one Williams syndrome (WS) (Hocking et al. 2014). Three studies combined various aetiologies such as Down syndrome with other unknown syndromes (K. Lee, Lee, and Song 2016; K. J. Lee et al. 2014) or Down syndrome with autism spectrum disorder and pervasive developmental disorders (Iosa et al. 2014). In five remaining studies, the aetiology of the ID was not specified (Alyt Oppewal and Hilgenkamp 2017; 2018; Alyt Oppewal, Festen, and Hilgenkamp 2018; Salb et al. 2017; Shieh et al. 2016). Twelve studies provided information on the level of ID (Table 2).

The studies covered a wide range of ages from 3 till 80 years of age. Sample sizes varied between 10 and 98 subjects. All of the included studies reported on overground walking and all except one (Shieh et al. 2016) explicitly stated that this was performed at preferred speed. In seven studies this was performed barefoot (Malatesta et al. 2013; Cimolin et al. 2014; Galli, Cimolin, Pau, et al. 2014; Galli et al. 2015; Galli, Cimolin, Rigoldi, et al. 2014; K. J. Lee et al. 2014; Salb et al. 2017), one study reported that subjects wore regular footwear (K. Lee, Lee, and Song 2016). The other studies provided no information on this topic (Table 2).

3.1.2 Spatio-temporal gait parameters

Sixteen studies provided data on spatio-temporal parameters using different methods. The GAITRite® electronic walkway was most often used (Abbruzzese et al. 2016; Djukic et al. 2016; Alyt Oppewal and Hilgenkamp 2017; Hocking et al. 2014; Horvat et al. 2013; K. J. Lee et al. 2014; Salb et al. 2017). A 3D video motion system (either Vicon or Elite BTS) was also frequently used (Cazalets et al. 2017; Malatesta et al. 2013; Cimolin et al. 2014; Galli et al. 2015; Salami et al. 2014). Three studies used inertial sensor technology (Iosa et al. 2014; O'Keefe et al. 2014; Shieh et al. 2016) while the remaining study measured gait speed by means of a chronometer during a 10 meter walk test (K. Lee, Lee, and Song 2016).

In *Down syndrome*, compared with a control group, three studies (Galli et al. 2015; Hocking et al. 2014; Salami et al. 2014) reported a significantly lower gait speed (DS: 0.66 – 1.05 m/s vs. control group CG: 1.10 – 1.30 m/s) together with a lower cadence (DS: 97 – 103 steps/min vs. CG: 109 – 115 steps/min) and a shorter step length (DS: 0.42 – 0.59 m vs. CG: 0.59 – 0.71 m). However, one study (Horvat et al. 2013) contradicts these findings reporting a higher gait speed, a higher cadence and a longer step length in Down syndrome compared to controls (Appendix 1, Table 1). In *Prader – Willi syndrome*, similarly, gait speed is significantly reduced (PWS: 0.88 – 0.98 m/s vs. CG: 1.03– 1.20 m/s), cadence is decreased (PWS: 105 steps/min vs. CG: 116 steps/min) and step length is significantly shorter (PWS: 0.51 m vs. CG: 0.63 m) compared to a control group (Malatesta et al. 2013; Cimolin et al. 2014). In other *syndrome-specific ID*, except for Rubinstein – Taybi syndrome (Cazalets et al. 2017), similar trends of low gait speed (Abbruzzese et al. 2016; Djukic et al. 2016; O'Keefe et al. 2014), low cadence (O'Keefe et al. 2014) and short step length (Abbruzzese et al. 2016) exist. In *Cri du Chat syndrome* (Abbruzzese et al. 2016), step width is significantly increased (CDC: 11.2 cm vs. CG: 8.5 cm). In patients with *Fragile-X associated tremor/ataxia*, duration of swing is decreased and duration of double support is significantly increased (O'Keefe et al. 2014) (Appendix 1, Table 1).

In a *general population with ID*, either spatio-temporal parameters of gait did not show significant differences compared to a control group (Iosa et al. 2014; Shieh et al. 2016) or no control group was available making it difficult to compare (Alyt Oppewal and Hilgenkamp 2017; K. Lee, Lee, and Song 2016; K. J. Lee et al. 2014; Salb et al. 2017).

3.1.3 Gait variability

Four studies report gait variability data either as coefficients of variation (Cazalets et al. 2017; Hocking et al. 2014; O'Keefe et al. 2014) or intra-subject standard deviations (Alyt Oppewal, Festen, and Hilgenkamp 2018).

In *syndrome-specific ID* populations, coefficients of variation for step length (Cazalets et al. 2017), stride length (Cazalets et al. 2017; O'Keefe et al. 2014), cadence (Cazalets et al. 2017; O'Keefe et al. 2014), step time (Hocking et al. 2014), stride time (Cazalets et al. 2017), step width (Cazalets et al. 2017) and gait speed (Hocking et al. 2014; O'Keefe et al. 2014) are significantly larger compared to a control group. Oppewal (Alyt Oppewal, Festen, and Hilgenkamp 2018) reported intra-subject standard deviations for spatio-temporal parameters in a *general ID population*, but this study did not have a control group, which makes it difficult to compare. Nevertheless, intra-individual variation in step width appears to be large (Appendix 1: Table 2).

3.1.4 Kinematic gait parameters

Three studies report kinematic data of which two are performed in Down syndrome (Galli et al. 2015; Galli, Cimolin, Rigoldi, et al. 2014) and one in Prader – Willi syndrome (Cimolin et al. 2014). All studies use a 3D video motion system with either the Davis marker set-up (Galli et al. 2015; Galli, Cimolin, Rigoldi, et al. 2014) or its adjusted version in Plug-in Gait (Cimolin et al. 2014).

In *Down syndrome*, compared to a control group, higher values are found for hip flexion at initial contact while hip extension in stance and hip range of motion in the sagittal plane are reduced (Galli et al. 2015). Knee extension in stance, maximal knee flexion in swing and knee range of motion in the sagittal plane are also reduced. At initial contact, the ankle is in plantar flexion instead of neutral (Galli et al. 2015), there is less ankle dorsiflexion in stance as well as reduced ankle plantar flexion at push-off and ankle range of motion in the sagittal plane (Galli et al. 2015). The mean foot progression angle is significantly more external (Galli, Cimolin, Rigoldi, et al. 2014). (Appendix 1: Table 3)

In *Prader – Willi syndrome*, differences are found around the ankle joint and to a lesser degree at the knee. There is a reduction in ankle plantar flexion at push-off and in ankle range of motion in the sagittal plane while knee flexion at initial contact is increased (Cimolin et al. 2014). (Appendix 1: Table 3)

3.1.5 Kinetic gait parameters

Three studies report on kinetic data in Down syndrome (Galli, Cimolin, Pau, et al. 2014; Galli et al. 2015) and Prader-Willi syndrome (Cimolin et al. 2014). In both populations only net joint moments and powers around the ankle are reported. Maximal ankle plantar flexion moment (DS: 0.99 (0.17) – 1.08 (0.38) Nm/kg; PWS: 1.02 (0.17) Nm/kg; CG: 1.29 (0.23) – 1.49 (0.25) Nm/kg) and maximal power generation at push-off (DS: 1.59 (0.96) – 1.60 (0.65) W/kg; PWS: 1.59 (0.51) W/kg; CG: 3.01 (0.52) – 3.73 (0.71) W/kg) are significantly reduced in both syndrome-specific ID populations. Since kinetic gait parameters are largely dependent upon walking speed, Cimolin (Cimolin et al. 2014) normalized maximal ankle joint power for speed and still found significantly smaller normalized ankle joint power in Prader-Willi syndrome compared to controls (PWS: 1.82 (0.55) W.s/kg.m; CG: 2.95 (0.80) W.s/kg.m).

3.1.6 Discussion and hypothesis generation

The results show significant gait deviations in the ID population with an underlying genetic syndrome. Main features are a reduced gait speed, short step length, increased step to step variability and a gait pattern with increased flexion in the knee joint and/or hip joint together with decreased ranges of motion at the ankle joint during the second and third rocker. Kinematic differences observed around the ankle joint coincide with reduced force and power generation at push-off. These observations are in line with the findings of Almuhtaseb (Almuhtaseb, Oppewal, and Hilgenkamp 2014).

In the general ID population however gait deviations are much less evident which contradicts the findings of Almuhtaseb (Almuhtaseb, Oppewal, and Hilgenkamp 2014). In her review she concluded that gait in the general ID population is also characterized by low gait speed and/or short step or stride length. Looking closer at the included studies, ID ranges from moderate to profound while in the studies included in this review ID in the general population is mostly mild to moderate (Appendix 1: Table 1). This might be a possible explanation for the observed differences.

Observed gait deviations in the ID population might be attributed to either physical characteristics or cognitive components. Physical characteristics are addressed in four studies looking at obesity in Prader-Willi syndrome (Cimolin et al. 2014) and Down syndrome (Galli et al. 2015) and looking at foot deformities in Down syndrome (Galli, Cimolin, Pau, et al. 2014; Galli, Cimolin, Rigoldi, et al. 2014). While these physical characteristics indeed have an effect on the gait, they do not seem to be the only determining factor. Cimolin (Cimolin

et al. 2014) found significant differences in gait pattern between Prader-Willi syndrome and the obese control group as well. Similarly, in the studies of Galli (Galli, Cimolin, Pau, et al. 2014; Galli, Cimolin, Rigoldi, et al. 2014) also the group with normal to high arch feet showed significant alterations in gait pattern, although less pronounced than in the flat feet group. (Appendix 1: Table 2 and 3) Therefore, while physical characteristics remain important, other factors such as the role of cognition cannot be ruled out.

The cognitive components in relation to gait are best studied using dual task paradigms. While data extraction focused on unperturbed walking, several studied included a dual-task paradigm (Abbruzzese et al. 2016; Alyt Oppewal and Hilgenkamp 2017; Hocking et al. 2014; Horvat et al. 2013). Results showed clear competition between the motor task (gait) and the dual task, whereby carrying out a secondary task will degrade motor performance to a larger extent in the ID group than in the healthy control group. (Appendix 2) Nevertheless, performance is dependent upon the kind of task and the population under investigation. For example, in Down syndrome, gait is mostly affected when the secondary task addresses the executive working memory while patients with Williams syndrome are more affected by tasks requiring set-shifting and visual-spatial processing (Hocking et al. 2014). Nevertheless it is clear that in ID populations, increased attentional resources are required during overground locomotion. The hypothesis has been formulated that gait is not a learned and pre-programmed motor task in these populations (Horvat et al. 2013). This hypothesis can be considered from the viewpoint of the atypical brain development concept affecting both cognitive and motor functions. We hypothesize that due to brain or brain function anomalies, control of gait has remained largely immature requiring more attentional resources. Possibly, this immature control is partially responsible for the observed immature features such as short and wide steps, increased variability and a flexed position of the lower limbs (A Hallemans, De Clercq, and Aerts 2006; A Hallemans et al. 2005).

3.2 Protocol development.

Several gait analysis methods have been developed and applied in clinical practice. Depending on the outcome of interest, a variety of measuring devices are selected to develop gait analysis protocols. When spatio-temporal parameters and gait variability are the only outcomes needed, electronic walkways or inertial sensors are feasible. Electronic walkways such as the GAITRite® can provide quick and accurate measurements and are suitable for children with motor disorders (Wondra, Pitetti, and Beets 2007). Inertial sensors enable evaluation

of a large number of steps outside of a hospital or research laboratory setting. Although spatio-temporal parameters are relevant to detect functional deviations in patients' gait, they do not provide further information on body motion and muscle function. This information however is often necessary to evaluate and treat gait problems and can be measured using adequate methods of body motion analysis during gait. Two general categories of such gait analysis methods exist: quantitative measurements using instrumented gait analysis (IGA, also referred to as three dimensional gait analysis) and observational assessments using video gait analysis (VGA). In the first category, three types of devices are used: image processing tools, floor sensors and wearable sensors, extensively described in literature (Muro-de-la-Herran et al. 2014).

To obtain valid and reliable data through gait analysis, a standardized measurement protocol is essential (Baker 2006; Toro, Nester, and Farren 2003). The use of gait analysis in children with ID is not common and standard protocols may be challenging for this population. Therefore in this section we will provide an overview of established IGA and VGA protocols and discuss their benefits and challenges in this population.

3.2.1 General gait analysis protocol

Standard gait analysis protocols consist of the same basic elements. Recordings start with a static trial which provides information on the standing posture of the patient and allows calibration of the marker model in instrumented gait analysis. Afterwards, dynamic overground walking trials are performed on a sufficiently long walkway. The patient should walk at self-selected walking velocity in a manner that is representative for their usual gait. Instructions on how to walk should be avoided in order to evoke a spontaneous pattern, but corrections are made when the child starts to show an undesirable gait such as running or excessive looking around and marching in a funny way. Gait analysis sessions should include structured physical examination for joint range of motion, muscle length, muscle strength and selectivity, spasticity and other clinical features needed for thorough interpretation of the gait analysis data (Desloovere et al. 2006).

Table 3

Overview of the different methods of gait analysis with their strengths, weaknesses and possible indications

	VIDEO GAIT ANALYSIS	INSTRUMENTED GAIT ANALYSIS
General	Recording of static posture and dynamic walking On a sufficiently long walkway (8 – 10m) at self-selected speed In three anatomical planes Barefoot and/or with shoes, orthotic devices or walking aids Combined with structured physical examination	
Modalities	**Core protocol:** Sagittal Coronal **Extended protocol:** Transversal (if available) Normal and close-up Goniometry Observational gait assessment tools	**Core protocol:** Spatiotemporal data Kinematic analysis Kinetic analysis Video data **Extended protocol:** Muscle activation patterns Foot pressure analysis
Strengths	Low budget User friendly Qualitative description Estimate of kinematics	Accurate Reliable Repeatable Quantitative data
Weaknesses	Projection errors Dependent on experience of the observer Deprived visibility in the transverse plane Less consistent than instrumented gait analysis	Longer session duration Good patient cooperation necessary Discomfort for patient Expensive equipment High level of expertise of assessors needed Specific knowledge for data interpretation required
Indications	Very young children, less cooperative children due to deprived cognitive abilities or behavioural problems, frequent monitoring in between IGA sessions	Planning and follow up of surgery and orthotic devices

3.2.2 Instrumented gait analysis

A general consensus on optimal IGA methods exists (Baker 2006) and detailed description lies beyond the scope of this review. In our centre, the gait laboratory (Multidisciplinary Motor Center Antwerp, M²OCEAN) is equipped with eight Vicon T10 cameras (100fps, 1 Megapix), Vicon Nexus, Bodybuilder and Polygon software, three AMTI type OR 6-7 force plates (1000fps), one Accugait force plate (1000 fps) and a 16 channel telemetric wireless EMG system (Aurion Zerowire). Retroflective markers are placed on bony landmarks following the PlugInGait Lower Limb marker model, which enables the quantification of pelvic position as well as hip, knee and ankle joint angles in all three anatomic planes. The lower limb model is preferred over full body models to reduce the number of markers, as these are experienced as disturbing by many children with ID. The combination of the optoelectronic tracking system and force plates allows the calculation of spatio-temporal data and the quantification of body segment and joint movements (kinematics) combined with the forces that cause these movements (kinetics), the core measurements of IGA. Simultaneous video registration provides a visual control and quality check. Additional measurement modalities can be added into an extended protocol if desired and achievable, as discussed further on and presented in table 3. Integrated dynamic EMG recordings allow the analysis of muscle activation patterns during walking. The preparation of the skin and application of electrodes takes more time and is uncomfortable for some children with ID. Therefore EMG recordings are left out of the core protocol to reduce the burden for the patient. Foot plantar pressure distribution measurement systems are additionally available for specific purposes.

Walking trials are repeated until at least three representative strides for each leg are recorded. A “clean” foot strike on a force plate is required for the collection of kinetic data. Targeting force plates is not representative for usual gait, therefore the child’s attention should not be drawn towards the force plates. In children who are less cooperative, it may not be possible to repeat trials until all selected strides contain reliable kinetic data. For children who make too small or shuffling steps, clean foot strikes on force plates are impossible. The collection of reliable kinematic data is prioritized over kinetic data. Kinetic data are only computed in case reliable foot strikes on force plates occurred. In case a child usually walks with orthotic devices, static and dynamic recordings are repeated with the child wearing their devices using the same marker placement.

The collected data are processed afterwards to provide data in an appropriate format for clinical interpretation. Spatio-temporal parameters, kinematic and kinetic time profiles and, if available, muscle activation patterns are reported. Age-related reference values of

typically developing children (mean +/- 1SD) are provided for comparison. Consistency plots, containing kinematic and kinetic data for up to six trials of the same side, are presented to assess the level of variability within the child's gait pattern. In case there is general variability across all graphs with an average trial to trial variability above 20°, caution is needed for the interpretation, as isolated gait trials are less representative for the child's overall gait pattern. Comparison reports are made in which barefoot trials and trials with shoes and orthotic devices are plotted together to evaluate the impact of the device on the gait pattern. Similarly, trials of consecutive sessions of the same child are brought together to assess the evolution of gait problems over time.

The most important strengths of IGA are its high reliability and accuracy, making it the gold standard for gait analysis. In their systematic review, McGinley et al. (McGinley et al. 2009) found that intra-rater reliability indices were typically higher than .80 in the sagittal plane (except for pelvic tilt), and slightly lower in the coronal and transversal plane (> .70 and <.70 respectively). Measurement errors were lower than 4° in the sagittal plane and around 2° in the coronal plane, smaller than what is considered a clinically important difference (McGinley et al. 2009). Moreover, Kawamura et al. proved that IGA is significantly more accurate in the detection of gait deviations than comparable VGA (Kawamura et al. 2007).

3.2.3 Video gait analysis

Limited studies have proposed VGA protocols as an accessible alternative to IGA (Rathinam et al. 2014) and recording methods are less extensively discussed. In our VGA protocol, two video cameras are positioned next to the walkway: one perpendicular and one parallel to the line of progression, providing sagittal and coronal plane observations respectively. A top view camera could additionally provide transverse plane images, but visibility in this plane is especially deprived. Two extra cameras can be added, zooming in on the patient's feet to provide close-up images (table 3).

Various observational gait assessment tools have been established to standardise the interpretation of VGA data in paediatric populations (Rathinam et al. 2014; Toro, Nester, and Farren 2003). The best results on reliability and validity assessments were found for the Edinburgh Visual Gait Score (EVGS) (Rathinam et al. 2014). This tool evaluates trunk, pelvis, hip, knee and ankle in the three anatomical planes using a three-point ordinal scale. However, observational gait assessment tools are highly dependent on the experience of the rater (Ong, Hillman, and Robb 2008) and intra-rater reliability is lower than in IGA (0.25 to 0.79). Furthermore, these tools were all designed and validated in populations of children

with CP and further research on their applicability in children with ID is needed.

The strength of VGA is its accessibility because of the low cost and user friendliness, both for the patient and the assessor. VGA provides an opportunity for more subjective qualitative description of the gait pattern. Also quantitative estimates of joint angles at specific points of the gait cycle can be made using goniometry. Custom-made software is available for this purpose (Grunt et al. 2010). However, these estimates are prone to projection errors and are less reliable than IGA. Video-based markerless motion capture systems are being developed, but more research is needed to improve their accuracy and applicability in clinical gait analysis (O'Keefe et al. 2014).

3.2.4 Considerations

The choice of adequate method and measurement modalities depends on the clinical goal, the available resources and the abilities of the patient.

The main goals of clinical gait assessment are the identification of gait deviations and the evaluation of their progress over time, in order to optimize the treatment plan. VGA may be sufficient to perform early follow-up of gait development and detect potential delay. Nevertheless, IGA is more adequate in detecting primary problems and compensatory strategies. VGA already offers insight in gait pathology and is helpful to establish a basic treatment plan. However, IGA is advised to guide clinical decision making and follow up after intervention when more complex treatment options are considered such as orthotic devices, orthopaedic surgery or botulinum toxin injections (Wren et al. 2011).

Very decisive in selecting the adequate protocol are the available resources. Not only does IGA require a fully equipped laboratory, its accuracy is also highly dependent on the experience of the staff that operates it and the processing and interpretation of IGA data requires training (Baker et al. 2016). Therefore VGA may offer a more user friendly and low cost alternative when these requirements are not met.

In a population of children with ID, the argument of the abilities of the child becomes especially important. Standard IGA procedures take up to two hours and demand a certain level of cooperation of the patient. If a child with behavioural problems is not able to sit still during preparations (electrode and marker placement) or if they pull the markers off, no reliable data can be obtained. In such cases, VGA is probably more appropriate. Furthermore, a child should be able to carry out simple instructions to walk in a straight line in a representative way, which might be easier in the less distractive setting of VGA than in IGA. The extensiveness

of the protocol of IGA influences the duration of a session and thus the burden for the patient. Within a reduced or extended protocol, duration of a session will further depend on the number of trials collected to assess consistency, the number of attempts needed to obtain clean foot strikes and the number of different situations (barefoot, orthotics, walking aids) that need to be analysed.

3.3 Case example of a patient with Dravet Syndrome.

Dravet Syndrome is a rare and severe form of drug resistant epilepsy and developmental delay with intellectual disability and behavioural problems (Ceulemans 2011) caused by a genetic mutation in *SCN1A*. A variety of gait characteristics have been reported in literature with crouch gait being the most observed gait pattern (Rilstone et al. 2012; Rodda et al. 2012). Other observed patterns include parkinsonian and cerebellar gait (Fasano et al. 2014). The cause of crouch gait is multifactorial and may include muscle weakness, spasticity, contractures or lever arm dysfunction (Kedem and Scher 2016). Clinical examination findings on these factors were inconsistent in patients with Dravet syndrome.

This case study presents a girl, diagnosed with Dravet Syndrome, who consulted our facility at the ages of 4y4m, 6y0m, 7y2m and 8y2m for instrumented gait analysis, walking barefoot without aids (See Appendix 3: Polygon Viewer). Due to young age and limited cooperation an extended instrumented protocol was not possible in every session and high quality trials were sometimes difficult to collect (in Figure 2 a trial with artefact had to be used due to lack of high quality trials).

3.3.1 Patient history, developmental assessment and physical examination

Patient history showed near normal development during the first year of life but a rapid delay thereafter. The milestone of independent sitting was acquired at the age of 7 months. Developmental age at 12 months was assessed with the Bailey Scales of Infant Development – II (BSID-II-NL) and was normal. However, a strong delay was observed in acquiring the milestone of independent walking, at an age of 36 months. At the age of 26 months, developmental age was only 15 months (BSID-II-NL, cognitive subscale) and also motor developmental age was delayed reaching only 12 months (BSID-II-NL, motor subscale).

A standardized physical examination was performed at the ages of 6y0m, 7y2m and 8y2m.

The most obvious finding is a severe pes planovalgus of both the left and right foot, already at the age of 6y0m, for which insoles were prescribed. Starting at the age of 7y2m internal rotation of the hips in stance is observed, becoming more severe at the age of 8y2m leading to "kissing knees". Femoral anteversion is slightly increased, especially at the left side (20° at age 6y0m going up to 40° at age 8y2m). Hamstrings are fairly short (popliteal angle deficit of 30° (L,R) at age 6y0m going up to 35°(L) and 45°(R) at age 8y2m) while calf muscles appear elongated (large passive ankle dorsiflexion range of motion of 15°-20° with the knee extended).

3.3.2 Spatio-temporal analysis

Dimensionless gait speed was highly variable within and between all sessions ranging from reduced (>2SD with reference to age-related TD children) at the age of 7y2m (0.24±0.05), over slightly reduced (>1SD with reference to age-related TD children) at the age of 4y4m (0.29±0.07) and 8y2m (0.37±0.04s) to normal at the age of 6y0m (0.48±0.05). This is in line with literature where reduced to normal gait speed and high variability is reported in patients with ID (Almuhtaseb, Oppewal, and Hilgenkamp 2014; Galli et al. 2015; Hocking et al. 2014; Salami et al. 2014). Dimensionless step length is reduced in three out of four sessions (0.50±0.09 – 0.64±0.08 x leg length) with more variability than in TD children. Only at 6y0m dimensionless step length (0.77±0.10 x leg length) was within normal values. A high to slightly increased cadence is seen at ages of 4y4m and 6y0m (152±27 steps/min and 158±7 steps/min) with very high variability at 4y4m, where at 7y2m cadence is slightly reduced (112±12 steps/min) and at 8y2m it is within normal values (131±8 steps/min). This high cadence is in contradiction with literature(Cimolin et al. 2014; Galli et al. 2015; O'Keefe et al. 2016) and might indicate that at a young age, she is still able to compensate for the short step length in order to maintain a functional gait speed.

3.3.3 Kinematics

At the *hip* (Figure 2; Appendix 3) normal to increased flexion at IC and slightly reduced extension at terminal stance is seen at all sessions with high variability within sessions, a typical feature of ID gait (Almuhtaseb, Oppewal, and Hilgenkamp 2014). Due to an increased hip flexion during swing, this does not lead to a reduced sagittal hip RoM.

At the *knee*, increased knee flexion (range 12-26°) at IC contact was seen at all occasions. Normal shock absorption (increased knee flexion during loading response) was present in most of the trials. At terminal stance knee extension was reduced in most trials and normal

in very few trials (range 5-25°), again in line with literature and variable within each session.

At the *ankle* (Figure 2; Appendix 3), in contrast to literature on gait in patients with ID, where a plantar flexed IC was often observed, a neutral position at IC was seen at all sessions. However, subsequent plantar flexion during first rocker was often absent. Second rocker showed highly variable patterns over all sessions, sometimes with a lack of tibia progression (horizontal), sometimes with plantar flexion (reversed second rocker) and sometimes with increased dorsiflexion. Push off was mostly normal but at the age of 8y2m, a decreased RoM during push off was observed (Figure 3 C). During swing, often a plantar flexion was seen at the end of swing that affected foot clearance only in few occasions.

Foot progression angle (Figure 2; Appendix 3), was again highly variable, but more often increased externally than increased internally rotated.

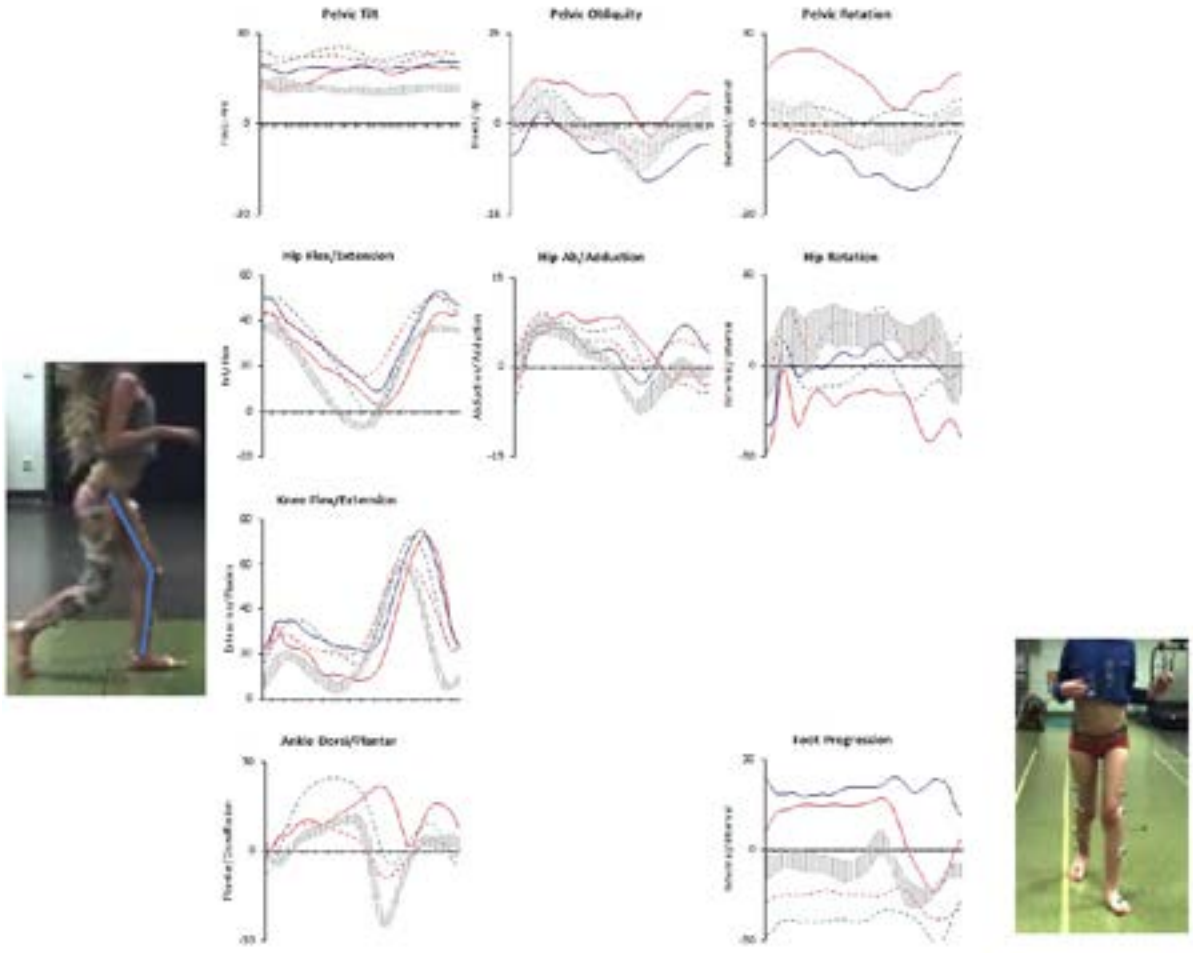

Figure 2. Kinematic analysis of one patient at age 4y4m (solid lines) and 6y0m (dashed lines). Mean joint angular time profiles, normalized to 100% of the gait cycle; red = left, blue = right; grey shaded area represents normative joint angular time profiles of typically developing children.

3.3.4 Kinetics

Collection of valid kinetics is a challenge in children with ID. Nevertheless, we were able to collect at least one trail per side per session.

Internal net joint extension moment of hip and knee was decreased at terminal stance in all four sessions. At the ankle, internal net joint plantar flexion moment was consistently decreased and ankle plantar flexion power at push off was only half of normal values in all trails in all sessions (Figure 3; Appendix 3).

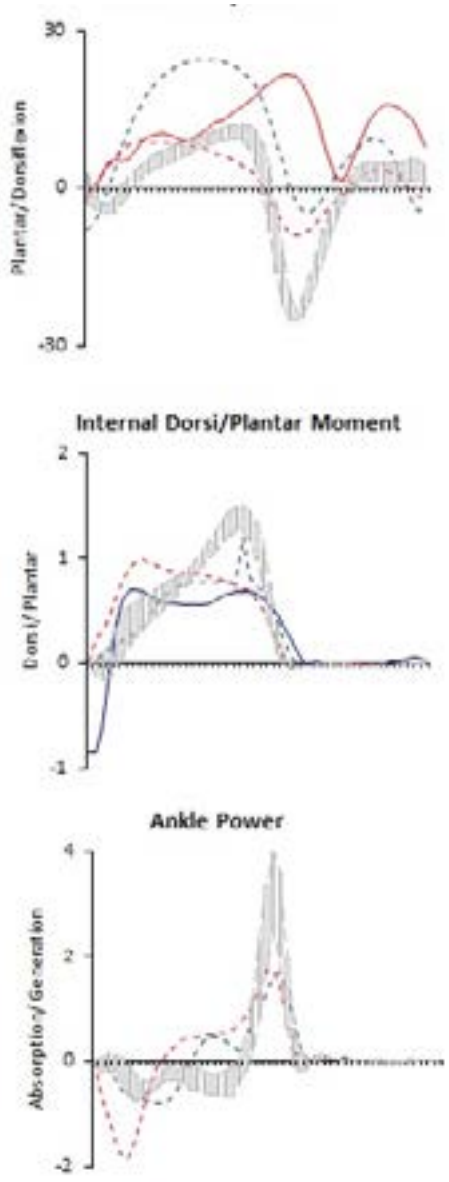

Figure 3. Kinetic analysis of one patient at age 4y4m (solid lines) and 6y0m (dashed lines). Mean joint angular time profile, net joint moment and net joint power of the ankle joint in the sagittal plane, normalized to 100% of the gait cycle; red = left, blue = right; grey shaded area represents normative joint angular time profiles of typically developing children.

3.3.5 Muscle activation patterns

EMG collection was difficult in this child and muscle activation patterns could only be evaluated at the ages of 6y0m and 7y2m. Prolonged activity during midstance is observed in the medial and lateral hamstrings as well as in the m. Rectus femoris and m. Vastus lateralis leading to co-contraction. Distally, gastrocnemius muscle is active too early in stance, leading to co-contraction with m. Tibialis anterior.

3.3.6 Clinical implications

Kinematic and kinetic data suggest the progressive development of a crouch gait pattern. The occurrence of hamstrings shortening is of concern as well as the increasing internal rotation of the hips. The interaction between these physical characteristics and the deviant gait pattern might lead to a vicious circle of increasing crouch. Crouch gait is a severe gait deviation that, due to the high amount of muscle work required, is very exhausting and can dramatically limit mobility. Therefore, at the age of 7y2m a rigid ankle-foot orthosis was prescribed to enhance correct knee alignment at initial contact. At first re-evaluation, indeed, knee angle at initial contact was less flexed when walking with the ankle-foot orthosis than walking barefoot. On the other hand, ankle motion is limited and power generation at push off might be even further compromised. Long term follow-up is necessary to evaluate the potential benefits and risks of this orthotic intervention.

4. Discussion

The aim of this review was to establish an overview of the gait features that are common in a population with ID as well as discuss potential benefits and challenges of performing instrumented gait analysis in patients with ID. For this purpose, an update of a previously published literature review was performed (Almuhtaseb, Oppewal, and Hilgenkamp 2014). In accordance with the original search strategy, this was limited to only one database, i.e. Pubmed, possibly reducing the comprehensiveness of the results.

In a population with ID we need to be aware that both cognitive and physical components can contribute to a deviant gait pattern. The usefulness of a clinical gait analysis in this population is that it allows clinicians to objectify the relationship between physical characteristics and gait features (Baker et al. 2016; Desloovere et al. 2006). While it is much more difficult to amend to gait deviations arising from poor cognition, physical characteristics are amenable to treatment. To do so, information on kinematics of gait, and preferably also information on

kinetics of gait and muscle function is required.

In our case example, significant gait deviations were found that are also reported in the literature on the ID population with genetic syndromes (Almuhtaseb, Oppewal, and Hilgenkamp 2014), such as a reduced gait speed, decreased step length, increased step to step variability (Abbruzzese et al. 2016; Cazalets et al. 2017; Malatesta et al. 2013; Alyt Oppewal and Hilgenkamp 2018; Cimolin et al. 2014; Galli et al. 2015; Hocking et al. 2014; O'Keefe et al. 2016; Salami et al. 2014) and increased flexion in the knee and hip joint along with reduced moments and power generation at push-off. Despite its challenges, gait analysis contributed to clinical decision making in this child, i.e. the prescription of ankle foot orthoses which led to improved extension in stance. It cannot be ruled out that cognition (Houwen et al. 2016; Vuijk et al. 2010) and competition for attentional resources (Hocking et al. 2014) as well as motivational aspects also played an important role in determining the gait pattern as the flexed gait pattern observed in this child is also frequently observed in other populations with ID such as Prader-Willi syndrome (Cimolin et al. 2014) and Down syndrome (Galli et al. 2015). But on top of these common features of ID gait, clinical gait analysis pointed towards rotational deformities and muscular contractures that appeared to worsen with increasing age. A mutual interaction between these physical characteristics and the flexed gait pattern is plausible and concern is that the child would enter a vicious circle of increased flexion during gait, leading to crouch gait, and worsening rotational deformities. Although at an early age it was virtually impossible to distinguish cognitive from physical components affecting gait, follow-up through clinical gait analysis showed that physical components came to the forefront when the child grew older and warranted treatment.

As mentioned before, obtaining a good quality IGA in children with ID is a challenge. Sometimes, this results in less reliable data due to difficult marker placement and/or difficult behavior. The recorded gait pattern should represent gait in daily life but in children with behavioral problems and low IQ, the lab setting can largely affect their gait. This can be further aggravated by attaching markers and electrodes to their skin. Furthermore, touching of markers may lead to artefacts. Also clear strikes on the force plate are not easy to obtain. Sometimes a child performs 20 or more gait trials and we only obtain good kinetic data in one.

In extremely challenging cases, or in young children, it might therefore be wise to opt for a standardized VGA protocol. Benefits of the VGA protocol are the low cost and the user friendliness. Duration of a session is dramatically reduced which promotes the cooperation of children with difficult behaviour. While VGA does not provide the accuracy and reliability of

IGA, it is often sufficient to detect whether gait deviations exist and follow their progression over time. In case severe deteriorations in gait or in physical characteristics are observed, an IGA can be considered. When a child is already familiar with the lab setting from previous VGA, improved cooperation and better quality IGA are expected. With our case example we have shown that, although challenging, good quality data can be obtained.

While not easily amenable to treatment, it might be interesting to obtain information on the cognitive load required to walk. This can be done by dual task paradigm in which case spatio-temporal parameters are considered as primary outcome measures. As discussed before, spatio-temporal parameters provide information on the functionality of the gait pattern and thereby (partially) reflect functioning in daily life. In these cases, use of gait mats (e.g. GaitRite ®) or inertial sensors (with accompanying software e.g. MoveMonitor and MoveTest, McRoberts), can be a good choice because of their limited processing time and direct availability of data.

5. Conclusion

Gait analysis has substantial value for patients with ID. In this population, both cognitive and physical components can contribute to a deviant gait pattern. Gait analysis allows clinicians to objectify the relationship between physical characteristics and gait features. The choice of adequate method and measurement modalities, being VGA or IGA, should depend on the clinical goal, the available resources and the abilities of the patient.

Appendix 1: Gait characteristics in intellectual disabilities (ID) during unperturbed overground walking

Table A1.1 Spatio-temporal parameters: mean (standard deviation)

Authors	Population	gait speed (m/s)	step time (s)	cadence (steps/ min)	step length (cm)	normalised step length	stride length (cm)	step width (cm)	stance (%)	swing (%)	double support (s)	double support (%)
Abbruzzese LD et al. 2016	CDC	0.88 (0.30)		135 (30)	38.5 (8.3)			11.2 (5.8)				29.5 (9.0)
	CG	1.02 (0.12)		113 (18)	54.7 (10.4)			8.5 (3.3)				26.5 (3.5)
Cazaletts et al. 2017	RTS			123 (16)		0.4 (0.05)						
	CG			115 (8)		0.5 (0.03)						
Cimolin et al. 2014	PWS	0.88 (0.09)		106 (5)		0.48 (0.04)			60.7 (1.6)			
	OCG	1.03 (0.07)		116 (5)		0.76 (0.05)			62.2 (1.3)			
	CG	1.20 (0.17)		117 (5)		0.80 (0.04)			59.6 (1.5)			
Djukic et al. 2016	RS	0.627										
Galli et al. 2015	DS not obese	0.71 (0.32)		97 (23)		0.33 (0.08)			59 (5.4)			
	DS obese	0.73 (0.23)		96 (15)		0.31 (0.08)			63.7 (3.5)			
	CG	1.1 (0.21)		115 (5)		0.88 (0.21)			59.5 (1.5)			
Hocking et al. 2014	DS	1.05 (0.26)	0.58 (0.08)	103	59.1 (4.2)			12.2			0.33 (0.08)	
	WS	1.12 (0.18)	0.54 (0.05)	111	59.5 (2.3)			11.9			0.30 (0.06)	
	CG	1.3 (0.14)	0.55 (0.05)	109	70.9 (2.7)			8.6			0.27 (0.06)	
Horvat et al. 2013	DS	1.30 (0.10)	0.52 (0.02)	115	67.3 (6.4)			9.0	64 (0.02)		0.24	
	CG	0.95 (0.24)	0.56 (0.09)	107	53.1 (10.1)			13.6	71 (0.13)		0.31	
Iosa et al. 2014	ID	1.20 (0.28)										
	CG	1.37 (0.26)										
Lee et al. 2016	ID1	0.99 (0.33)										
	ID2	0.94 (0.34)										

Authors	Population	gait speed (m/s)	step time (s)	cadence (steps/ min)	step length (cm)	normalised step length	stride length (cm)	step width (cm)	stance (%)	swing (%)	double support (s)	double support (%)
Lee et al. 2014	ID1	0.91 (0.19)	0.57 (0.04)	135 (8)	50 (9)							
	ID2	0.89 (0.22)	0.55 (0.44)	135 (9)	49 (12)							
Malatesta et al. 2013	PWS	0.98 (0.03)	0.53 (0.01)	115 (2.4)	51 (1)							26
	CG	1.20 (0.02)	0.53 (0.01)	115 (1.8)	63 (1)							24
O'Keefe et al. 2016	FXATS +	1.09 (0.18)		99 (12)						37.5 (2.2)		24.9 (4.4)
	FXATS -	1.31 (0.20)		114 (9)						38.6 (1.8)		22.8 (3.8)
	CG	1.36 (0.16)		116 (9)						40.7 (1.8)		18.5 (3.6)
Oppewal et al. 2017. 2018a. 2018b	ID	1.18 (0.23)	0.56 (0.05)	108 (23)	65.2 (10.1)			11.9 (3.5)	58.9 (2.0)	41.0 (2.0)		18.1 (4.1)
Salami et al. 2014	DS	0.66			42.2			19.9				
	CG	1.20			58.6			15.2				
Salb et al. 2017	ID	0.86 (0.29)		101 (14)			102 (27.9)					
Shieh et al. 2017	ID	1.14 (0.47)	0.48 (0.06)	125								
	CG	1.17 (0.57)	0.50 (0.03)	120								

Underlined values differ significantly from CG. CG = control group, CDC = Cri Du Chat syndrome, PWS = Prader Willi syndrome, RS = Rett syndrome, DS = Down syndrome, WS = Williams syndrome, ID = intellectual disability of different causes, FXATS = Fragile X associated Ataxia and Tremor

Table A1.2

Gait Variability as intra-subject coefficient of variation (%)

Authors	Population	COV step length	COV stride length	COV cadence	COV step width	COV stride time	COV step time	COV speed
Cazalets et al. 2017	RTS	8,8	7,7	5,8	18,9	6,3		
	CG	2,8	2	1,8	6,7	1,8		
Hocking et al. 2014	DS						6,99	8,88
	WS						4,73	6,78
	CG						3,47	4,15
O'Keefe et al. 2016	FXATS +		3,99	4,48				6,71
	FXATS -		2,07	2,36				3,23
	CG		2,25	2,36				3,08
Oppewal et al. 2018	ID	4,58*	4,04*		21,13*	3,57*	3,57*	5,99*

Underlined values differ significantly from CG. * COV were calculated from individual mean and standard deviation. CG = control group, RTS = Rubinstein – Taybi syndrome, DS = Down syndrome, WS = Williams syndrome, FXATS = Fragile X associated Ataxia and Tremor, ID = intellectual disability of various causes

Table A1.3

Kinematic parameters: mean (standard deviation)

		Sagittal					Frontal	Transverse		
Pelvis						**RoM°**	**RoM°**	**RoM°**		
Cimolin et al. 2014	PWS					7.12 (2.93)				
	CG obese					5.67 (3.46)				
	CG					1.61 (3.67)				
Galli et al. 2015	DS nonobese					4.69(3.07)	7.89(5.05)	13.08 (10.54)		
	DS obese					4.65 (1.91)	7.34 (6.25)	12.86 (10.66)		
	CG					1.61 (3.67)	6.01 (2.57)	10.72 (5.32)		
Hip		**IC°**		**minSt°**		**RoM°**	**RoM°**			
Cimolin et al. 2014	PWS	49.24 (15.94)		8.64 (10.78)		39.25 (6.86)				
	OCG	43.50 (11.23)		-3.46 (10.71)		43.45 (4.10)				
	CG	27.22 (7.54)		-11.92 (7.68)		45.92 (5.36)				
Galli et al. 2015	DS nonobese	36.30 (11.98)		0.38 (10.92)		37.16 (8.58)	12.94 (6.39)			
	DS obese	36.58 (14.44)		2.29 (8.98)		36.67 (9.55)	13.67 (6.22)			
	CG	27.22 (7.54)		-13.92 (7.68)		44.92 (5.36)	11.92 (6.13)			
Knee		**IC°**	**minSt°**		**maxSw°**	**RoM°**				
Cimolin et al. 2014	PWS	10.99 (6.29)	-0.49 (4.19)		55.84 (7.04)	56.75 (6.33)				
	CG obese	4.93 (7.25)	-2.2 (5.94)		54.84 (7.34)	58.23 (4.42)				
	CG	4.06 (6.63)	0.12 (3.82)		59.01 (6.18)	60.28 (6.31)				

		Sagittal					Frontal	Transverse		
Galli et al. 2015	DS nonobese	7.11 (11.68)	6.29 (11.49)		52.52 (8.31)	49.08 (9.57)				
	DS obese	5.94 (12.21)	5.21 (9.06)		51.34 (7.01)	44.63 (10.62)				
	CG	4.06 (6.63)	0.12 (3.82)		59.01 (6.18)	60.28 (6.31)				
Ankle & Foot Progression Angle		**IC°**	**maxSt°**	**minSt°**	**maxSw°**	**RoM°**		**Mean FPA°**	**FPA St°**	**FPA Sw°**
Cimolin et al. 2014	PWS	-1.61 (9.89)	13.59 (6.77)	-7.18 (11.83)	11.53 (9.61)	20.78 (5.04)				
	CG obese	-1.45 (7.26)	13.95 (3.34)	-15.85 (6.61)	5.08 (2.36)	29.81 (6.88)				
	CG	1.81 (4.87)	12.91 (5.97)	-18.98 (6.19)	8.63 (9.93)	27.72 (6.56)				
Galli et al. 2015	DS nonobese	-2.97 (5.81)	13.37 (9.05)	-4.74 (7.47)	8.91 (8.08)	17.56 (8.40)		-20.69 (11.71)		
	DS obese	-3.29 (6.60)	10.85 (7.16)	-4.59 (8.55)	4.65 (8.55)	15.99 (7.21)		-22.17 (15.19)		
	CG	1.81 (4.87)	19.91 (5.97)	-8.98 (6.19)	8.63 (9.93)	27.72 (6.56)		-14.88 (8.35)		
Galli et al. 2014b	DS normal/high arch								-15.05 (9.99)	-12.52 (8.02)
	DS low arch								-20.73 (10.48)	-21.85 (11.53)
	CG								-13.51 (3.64)	-16.12 (4.23)

Underlined values differ significantly from CG. CG = control group, PWS = Prader Willi syndrome, DS = Down syndrome; RoM = range of motion, IC = initial contact, min = minimum, max = maximum, St = stance, Sw = swing, FPA = Foot Progression Angle

Appendix 2: Gait characteristics in intellectual disabilities (ID) during dual tasking

Table A2.1

Spatio-temporal parameters comparing dual tasks to single tasks: mean (standard deviation) and intra-individual variability

Author			gait speed (m/s)	Step time (s)	cadence (steps/min)	step length (cm)	Step Width (cm)	double support (s)	COV speed	COV step time	SD step length
Abbruzzese et al. 2016	CDC	Single task	0.88 (0.30)		134.6 (29.7)	38.5 (8.3)	11.2 (5.8)	29.5 (9.0)%			
		Tray	0.77 (0.25)		127.1 (23.4)*	37.1 (8.9)	12.1 (4.3)	30.8 (8.9)%			
		Pitcher	0.66 (0.19)*		119.9 (23.9)*	33.3 (8.2)*	10.9 (5.6)	35.4 (6.4)%*			
	CG	Single task	1.02 (0.12)		112.8 (17.7)	54.7 (10.4)	8.5 (3.3)	26.4 (3.5)%			
		Tray	0.79 (0.19)*		98.1 (13.3)*	47.4 (10.6)*	8.9 (2.6)	31.3 (3.8)%*			
		Pitcher	0.84 (0.24)*		97.7 (14.2)*	50.8 (11.0)*	7.5 (4.0)	30.1 (4.4)%*			
Hocking et al. 2014	DS	Single task	1.05 (0.26)	0.58 (0.08)		59.0 (9.8)	12.2 (4.2)	0.33 (0.08)	8.9 (3.7)	6.9 (1.8)	
		Verbal fluency	*	*		*	ns	*	*	*	
		Digit span short	ns	ns		ns	ns	ns	ns	ns	
		Digit span long	ns	ns		ns	bs	ns	ns	ns	
	WS	Single task	1.12 (0.18)	0.54 (0.05)		59.51 (7.09)	11.95 (2.30)	0.30 (0.06)	6.8 (2.5)	4.7 (1.2)	
		Verbal fluency	ns	ns		ns	ns	ns	ns	ns	
		Digit span short	*	ns		ns	*	ns	ns	*	
		Digit span long	ns	ns		ns	*	ns	*	ns	
	CG	Single task	1.30 (13.85)	0.55 (0.05)		70.94 (6.26)	8.62 (2.69)	0.27 (0.06)	4.2 (1.9)	3.5 (1.7)	
		Verbal fluency	*	*		*	ns	*	*	*	
		Digit span short	*	ns		ns	*	ns	ns	*	
		Digit span long	ns	ns		ns	*	ns	*	ns	

Author			gait speed (m/s)	Step time (s)	cadence (steps/min)	step length (cm)	Step Width (cm)	double support (s)	COV speed	COV step time	SD step length
Horvat et al. 2013	DS	Single task	1.30 (0.10)	0.52 (0.02)		67.3 (6.4)	9.0 (1.4)	0.24 (0.02)			
		Plate & Cup	1.32 (0.09)	0.51 (0.02)*		67.8 (5.9)*	9.2 (1.5)*	0.23 (0.01)*			
		Tray & Cup	1.37 (0.16)	0.50 (0.02)*		68.9 (7.7)	9.2 (1.9)*	0.22 (0.01)*			
		Phone	1.24 (0.14)*	0.53 (0.02)		65.7 (7.4)*	9.7 (1.8)*	0.24 (0.02)			
		Buttoning shirt	1.23 (0.11)*	0.52 (0.02)		64.5 (6.1)*	10.7 (2.6)*	0.25 (0.02)			
	CG	Single task	0.95 (0.24)	0.56 (0.09)		53.1 (10.1)	13.6 (5.3)	0.31			
		Plate & Cup	0.95 (0.27)	0.57 (0.15)*		51.6 (11.7)	15.0 (5.9)*	0.35 (0.23)*			
		Tray & Cup	0.87 (0.25)	0.57 (0.17)*		46.6 (7.6)	14.8 (5.4)*	0.36 (0.26)*			
		Phone	0.77 (0.21)	0.61 (0.15)		44.7 (7.7)*	14.8 (5.8)*	0.41 (0.25)			
		Buttoning shirt	0.77 (0.26)	0.64 (0.30)		42.6 (8.8)*	15.0 (5.8)*	0.48 (0.50)			
Oppewal et al. 2017	ID	Single task	1.18 (0.23)	0.56 (0.05)	108 (10)	65.3 (10.1)	11.9 (3.5)	0.20 (0.06)	7.1 (2.8)	0.02 (0.01)	2.99 (0.98)
		Talking	*	*	*	*	ns	*	ns	ns	*

Asterisk (*) indicates significant difference with single task condition; CG = control group, CDC = Cri Du Chat syndrome, DS = Down syndrome, WS = Williams syndrome, ID = intellectual disability of different causes; COV = coefficient of variation, SD = standard deviation

Chapter 2

Gait deviations in patients with Dravet Syndrome: a systematic review

Chapter 2

Gait deviations in patients with Dravet Syndrome: a systematic review

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1. Abstract

Background: Dravet Syndrome is a rare developmental epileptic encephalopathy characterised by epileptic seizures, cognitive impairment and motor disorders. Gait is markedly impaired and could benefit from targeted intervention to improve quality of life for patient and caregivers.

Objective: To establish the state of the art regarding gait deviations in patients with Dravet Syndrome.

Methods: A systematic search was performed in Pubmed, Web of Science, Science Direct and Embase. Studies that assessed gait deviations in patients diagnosed with Dravet Syndrome using clinical observation, video gait analysis or three dimensional (3D) gait analysis and reported gait characteristics, spatiotemporal or kinematic outcomes were included. Screening, quality assessment and data extraction were performed by independent reviewers.

Results: Out of a total of 478 citations, nine articles were included. The total study population had an age range from 2.5 to 47 years. Three studies used clinical observation, three studies video analysis and three studies 3D gait analysis. Crouch gait was observed in about half of the population next to a variety of other gait deviations such as parkinsonian and cerebellar gait. Other findings included abnormalities in spatiotemporal parameters and kinematics, passive knee extension deficits, skeletal malalignment and neurological signs.

Conclusions: A variety of gait characteristics was observed with crouch gait being the most reported gait pattern. Inconsistency in methods and findings from clinical and instrumented evaluation impede thorough understanding of the causal mechanism and evolution behind these deviations.

PROSPERO registration number: CRD42017070370

2. Introduction

Dravet Syndrome, also called Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare developmental epileptic encephalopathy with an onset of severe epileptic seizures during the first year of life (Dravet 2011). Prevalence is estimated between 1/15.000 and 1/40.000 and at least 80% of the patients have a mutation in the sodium channel type I alpha subunit, *SCN1A* (Brunklaus et al. 2012; Wu et al. 2015). Characteristics are drug resistant epileptic seizures, cognitive impairment and motor disorders (Brunklaus et al. 2012). Stagnation or

decline in psychomotor development becomes evident before the age of two, with delayed development of gross and fine motor skills, language and cognitive abilities (Verheyen, Verbecque, et al. 2019; Wolff, Cassé-Perrot, and Dravet 2006; Brunklaus et al. 2012). Gait is markedly impaired which tends to worsen with patients' age, making them lean on others or use a wheelchair for longer distances (Rodda et al. 2012; Scheffer 2012; Dravet 2011). Hence gait problems aggravate the lack of independence and become a major concern for parents and caregivers (Camfield, Camfield, and Nolan 2016; Villas, Meskis, and Goodliffe 2017). While seizure control has been the principal issue in treatment of patients with Dravet Syndrome, attention to other problems such as gait disorders may as well improve quality of life for patient and caregivers (Ceulemans 2011). Orthopaedic interventions and rehabilitation programs could address motor problems and improve walking abilities of patients. Detailed evaluation of motor function and more specifically gait examination may be performed to guide therapy planning and form an important part of the patients' follow-up (Franki et al. 2015; Wren et al. 2011). Several methods for qualitative and quantitative gait examination exist. Clinical observation is usually performed during routine neurologic examination when a specialist observes the gait pattern of a patient. Video analysis refers to all methods that include video recording, which enables more repeatable examination, especially when standardized assessment tools are used (Rathinam et al. 2014). Instrumented three dimensional (3D) gait analysis provides a more objective and reliable evaluation of gait (McGinley et al. 2009). In addition to registration of time- and distance-related aspects of gait (spatiotemporal parameters), it quantifies body segment and joint movements (kinematics) often combined with the forces that cause these movements (kinetics) and muscle activity during walking (electromyography). It remains unclear to what extent gait evaluations are performed in populations with Dravet Syndrome and how gait deviations are identified so far. Therefore, this literature review aims to provide an overview of all studies on evaluation of gait in patients with Dravet Syndrome.

3. Methods

3.1 Sources

This systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009). The review protocol was predetermined and registered with the international prospective register of systematic reviews (PROSPERO, CRD42017070370). Three authors (AH, ITB and

LW) performed a systematic search in four databases on May 23, 2018 with an update on October 24, 2018. The included databases were Pubmed, Web of Science, Science Direct and Embase. The search query "(dravet syndrome OR severe myoclonic epilepsy) AND (gait OR locomotion OR walking)" was adapted to the specific needs of each database, as reported in table 1. EndNote X7™ (Clarivate Analytics) software was used to eliminate duplicates. A hand search for additional relevant publications was performed by consulting the reference lists of the included articles. If an article was not available, authors were contacted in order to obtain the manuscript.

Table 1
Detailed search queries per database

Database	Search details
Pubmed	((“epilepsies, myoclonic”[MeSH Terms] OR (“epilepsies”[All Fields] AND “myoclonic”[All Fields]) OR “myoclonic epilepsies”[All Fields] OR (“dravet”[All Fields] AND “syndrome”[All Fields]) OR “dravet syndrome”[All Fields]) OR (severe[All Fields] AND (“epilepsies, myoclonic”[MeSH Terms] OR (“epilepsies”[All Fields] AND “myoclonic”[All Fields]) OR “myoclonic epilepsies”[All Fields] OR (“myoclonic”[All Fields] AND “epilepsy”[All Fields]) OR “myoclonic epilepsy”[All Fields]))) AND ((“gait”[MeSH Terms] OR “gait”[All Fields]) OR (“locomotion”[MeSH Terms] OR “locomotion”[All Fields]) OR (“walking”[MeSH Terms] OR “walking”[All Fields])) AND “humans”[MeSH Terms]
Web of Science	TS = ((dravet syndrome OR severe myoclonic epilepsy) AND (gait OR locomotion OR walking))
ScienceDirect	(“dravet syndrome” OR “severe myoclonic epilepsy”) AND (gait OR locomotion OR walking)
Embase	((dravet AND syndrome) OR (severe AND myoclonic AND epilepsy)) AND (‘gait’/exp OR gait OR ‘locomotion’/exp OR locomotion OR ‘walking’/exp OR walking)

3.2 Study selection

The screening procedure in two phases was performed independently by three researchers (AH, ITB and LW). A priori formulated in- and exclusion criteria were applied to titles and abstracts in the first phase following the PICOS approach (Richardson et al. 1995). In case

of uncertainty or if no abstract was available, the full texts were obtained for the second screening phase. Studies were included when the population (P) consisted of human patients diagnosed with Dravet Syndrome without any age limit. As intervention (I), an assessment of gait by means of clinical observation, 2D video gait analysis or instrumented 3D gait analysis had to be performed. No comparison group (C) was required. Articles that had an outcome (O) in terms of gait characteristics, spatiotemporal parameters, kinematics, kinetics or electromyography were included. Original research using any type of study is considered relevant to answer the research question, therefore all study designs (S), except for books, reviews and meta-analyses were included. Occasional and subjective reports on gait problems in studies with a focus on genetics, pharmacology or behavioural problems were excluded. Language knowledge of the authors was restricted to English, Dutch, French and German. Articles in other languages were not included.

3.3 Data extraction and risk of bias

Data were extracted by the same three researchers (AH, ITB and LW) using a structured table including study design, population characteristics (number of participants, age, gender, diagnosis), measurement instruments and protocols and results on gait analysis and secondary outcomes. Risk of bias assessment was independently performed by two researchers (LW and PVdW) and the results were discussed until agreed upon. The Newcastle-Ottawa assessment Scale for cohort studies (NOS) was adapted for cross-sectional studies, selected from previous adaptations (Herzog et al. 2013). A maximum of five stars could be earned in two categories: selection and outcome (Appendix).

4. Results

4.1 Study selection

A total of 583 citations were identified in Pubmed (n=83), Web of Science (n=36), Science Direct (n=330) and Embase (n=134). After deduplication, 478 potentially relevant citations were screened. Eight citations were manually added for full text screening, of which none were found to be eligible. Full text assessment of thirty articles revealed nine articles that met the inclusion criteria (figure 1).

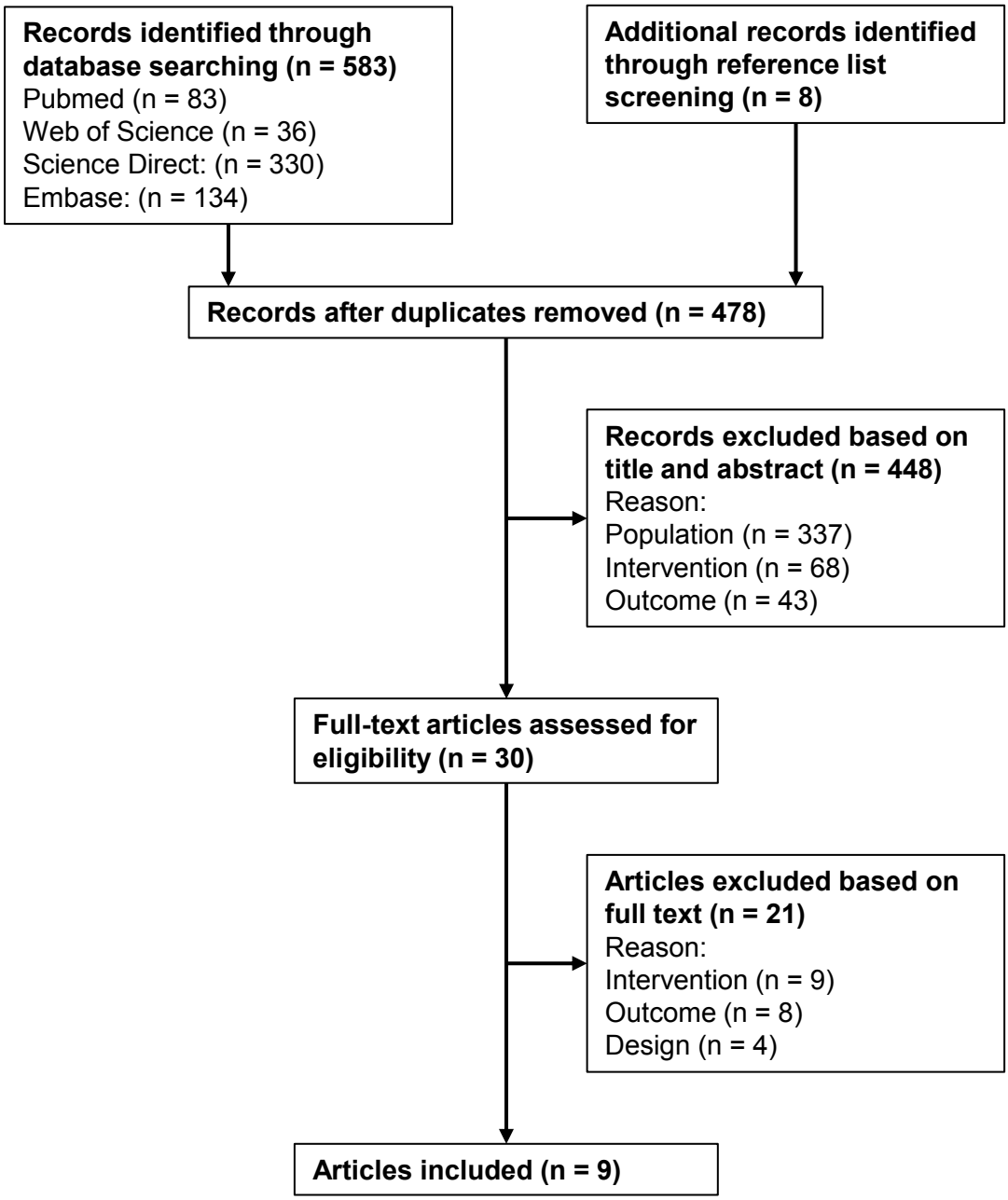


Figure 1. Study selection process

4.2 Study characteristics

Three full-length articles (Gitiaux et al. 2016; Rilstone et al. 2012; Rodda et al. 2012), two short notes (Aljaafari et al. 2017; Fasano et al. 2014) and four conference abstracts (Hallemans et al. 2016; Spagnolo et al. 2016; Verheyen et al. 2018; Wyers et al. 2017) were included. All studies used cross-sectional study designs. Two patient cohorts reappear in different studies. Rilstone et al. (2012), Fasano et al. (2014) and Aljaafari et al. (2017) included patients from the Hospital for Sick Children, Toronto, Canada (Fasano et al. 2014; Rilstone et al. 2012;

Aljaafari et al. 2017) and Hallemans et al. (2016), Wyers et al. (2017) and Verheyen et al. (2018) from the Antwerp University Hospital, Belgium (Hallemans et al. 2016; Verheyen et al. 2018; Wyers et al. 2017). The other research groups were situated in Australia (Rodda et al. 2012), France (Gitiaux et al. 2016) and Italy (Spagnolo et al. 2016). Patients with an age range from 2.5 to 47 years were included. Six studies examined mainly children and adolescents, whereas the other three included only adults (table 2).

4.3 Risk of bias

The quality of the studies varied between two and four stars on a total of five (table 2). All studies earned a star for representativeness of the sample, with three studies reporting a consecutive cohort and five studies using non-random sampling. Since no study justified the sample size, no stars were earned on this item. All but two studies described the ascertainment of diagnosis and earned a star. Outcome assessments and statistical tests were variable between all studies, explaining most of the variability in total number of stars (Appendix).

4.4 Primary outcome

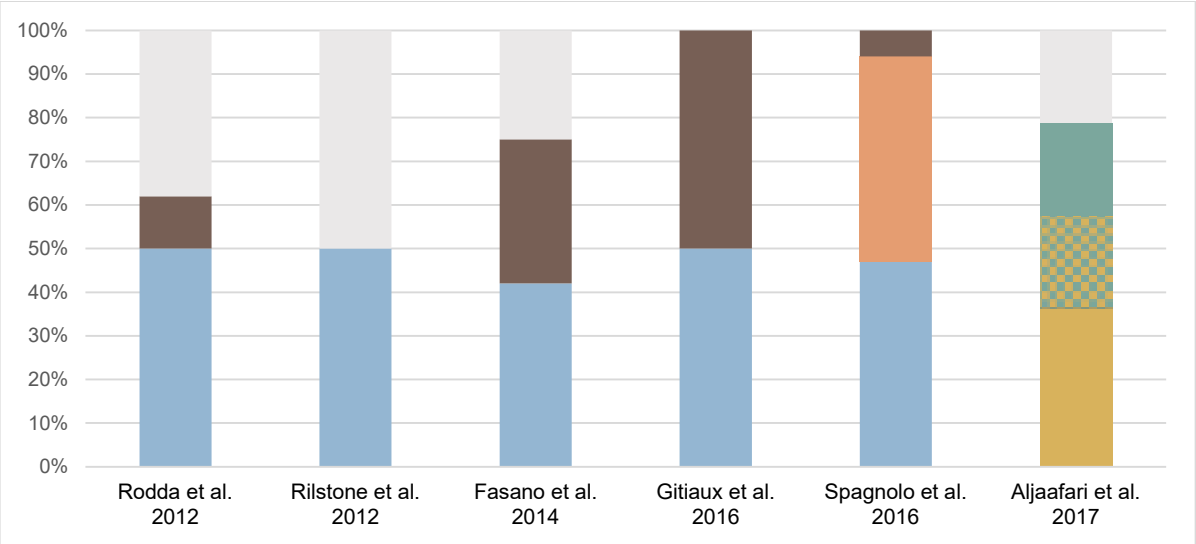
Gait was the primary outcome of this review and was assessed using different methods. Three studies evaluated gait by means of clinical observation (Aljaafari et al. 2017; Gitiaux et al. 2016; Rilstone et al. 2012), three studies used video analysis (Fasano et al. 2014; Rodda et al. 2012; Spagnolo et al. 2016) and three studies performed instrumented 3D gait analysis (Hallemans et al. 2016; Verheyen et al. 2018; Wyers et al. 2017) (table 2). Three types of outcomes on gait were described in the included studies. First, rather qualitative descriptions of gait patterns will be discussed, followed by descriptions of spatiotemporal parameters and finally gait kinematics. Since kinetics and EMG were not reported in the included studies, this will not be discussed.

4.4.1 Gait pattern description

Based on clinical observation (Aljaafari et al. 2017; Gitiaux et al. 2016; Rilstone et al. 2012) and video analysis (Fasano et al. 2014; Rodda et al. 2012), various gait patterns were described, as shown in figure 2. The terminology used for this description was not always defined. Rodda et al. (2012) observed a normal or variable sagittal plane gait pattern in children up to five years. Between ages six and twelve, half of the patients had developed a crouch gait pattern, defined by increased hip and knee flexion and ankle dorsiflexion throughout the

stance phase. In the subgroup of 13 years and older, eight out of nine patients walked in crouch. No definition of the variable gait pattern was reported, but the authors mentioned that ataxia, defined by wide-based gait, was rarely observed in the cohort (Rodda et al. 2012). Rilstone et al. (2012) observed crouch gait, defined by the presence of knee and hip flexion during stance or gait in five out of ten patients, progressively worsening with age. None of their patients exhibited gait ataxia (Rilstone et al. 2012). Fasano et al. (2014) recognized crouch gait without further specification, and other gait abnormalities such as small or shuffling steps, en-bloc turns and "slapping to the floor" steps (Fasano et al. 2014). In the study of Gitiaux et al. (2016), all patients showed gait disturbances and children older than six exhibited crouch gait, not further specified. No exact number of patients with this gait pattern was reported, but six out of twelve patients were older than six indicating that about half of the population exhibited crouch gait (Gitiaux et al. 2016). Spagnolo et al. (2016) identified two evenly distributed patterns: crouch gait and a pattern characterized by normal knee joint motion but increased ankle plantarflexion in preswing (Spagnolo et al. 2016). Furthermore, they observed forward lean of the trunk with anterior pelvic tilt in half of their population and knee hyperextension in one patient (Spagnolo et al. 2016). Aljaafari et al. (2017) observed parkinsonian gait and cerebellar gait in their population without reporting the definitions used. Parkinsonian gait, but not cerebellar gait, was significantly more present in their cohort of patients with Dravet Syndrome as compared to Lennox-Gastaut Syndrome (Aljaafari et al. 2017).

Figure 2. Percentage and definition of observed gait patterns in the included population per first author



Normal	Normal gait (Rodda, Rilstone, Fasano)
	No parkinsonian gait, no cerebellar gait (Aljaafari)
Other	Variable, not specified (Rodda)
	Small or shuffling steps, en bloc turns, “slapping to the floor” steps, irregular, reduced or absent arm swinging, tip toe gait, frequent stops, wide base, long steps or festination (Fasano)
	Gait disturbances, not specified (Gitiaux)
	Hyperextension of the knee (Spagnolo)
Cerebellar	Cerebellar gait, not specified (Aljaafari)
	Both parkinsonian gait and cerebellar gait (Aljaafari)
Parkinsonian	Parkinsonian gait, not specified (Aljaafari)
Normal knee, altered ankle	A pattern characterized by normal knee kinematics but altered ankle kinematics with increased plantarflexion in preswing (Spagnolo)
Crouch	Increased hip and knee flexion and ankle dorsiflexion throughout the stance phase (Rodda)
	The presence of knee and hip flexion during stance or gait (Rilstone)
	Crouch, not specified (Fasano, Gitiaux)
	Flexed knee associated with possible alterations of ankle kinematics (Spagnolo)

4.4.2 Spatiotemporal parameters

Several parameters can be calculated based on spatial and temporal measurements of gait. Also qualitative descriptions will be discussed in this paragraph, since only two authors reported spatiotemporal parameters. Fasano et al. (2014) based their findings on video observation and described small steps in seven out of twelve patients, long steps in one and a wide base in one other (Fasano et al. 2014). Hallemans et al. (2016) reported spatiotemporal parameters calculated through instrumented 3D gait analysis. A lower walking velocity (1.03±0.25 m/s), smaller strides (0.93±0.21 m), higher cadence (67±10 strides/min) and longer duration of stance (61±3%) were observed in children with Dravet Syndrome compared to age-matched typically developing children (Hallemans et al. 2016).

4.4.3 Kinematics

Kinematics study the position and motion of body segments and joints in the three anatomical planes. The participants from the Antwerp study cohort were tested using instrumented 3D gait analysis and compared to age-matched typically developing children based on mean kinematic parameters (Hallemans et al. 2016), mean kinematic time profiles (Wyers et al. 2017) and Gait Profile Scores (Verheyen et al. 2018) (table 3).

Mean pelvic internal rotation and external hip rotation were significantly increased (Hallemans et al. 2016). Concerning the hip, increased flexion was found at initial contact (Hallemans et al. 2016) during stance (Wyers et al. 2017) and in swing (Hallemans et al. 2016), as well as increased adduction in midstance (Hallemans et al. 2016). Increased knee flexion was measured in different parts of the stance phase (Hallemans et al. 2016; Wyers et al. 2017) and in swing (Hallemans et al. 2016). At the level of the ankle, increased dorsiflexion in stance (Hallemans et al. 2016), around push-off (Wyers et al. 2017) and in swing (Hallemans et al. 2016) were observed, as well as overall increased external rotation of the ankle (Wyers et al. 2017). In both studies, the standard deviations around the means were large (Hallemans et al. 2016; Wyers et al. 2017).

The kinematic time profiles of different joints were combined to calculate Gait Profile Scores (Baker et al. 2009) in the study of Verheyen et al. (2018). The authors considered scores as deviations when they exceeded two standard deviations of the scores in a reference group of typically developing children. Deviations were found in four out of twenty-nine patients for sagittal plane kinematics (combination of pelvis, hip, knee and ankle) and in five patients for coronal plane kinematics (pelvis and hip). For transverse plane kinematics (pelvis, hip and foot), deviations were found in fifteen patients (Verheyen et al. 2018). Secondary outcomes

Various secondary outcomes related to motor problems were reported in the included articles. The most relevant will be discussed in the next paragraphs and consisted of the evaluation of musculoskeletal integrity, neurologic signs and activities and participation.

Table 2
Description of included studies

First Author	Year	Journal, article type	City, Country	Sample size	Age range	Gender m/f	Diagnosis	Method of gait analysis	Additional investigation	Study quality
Rodda	2012	Arch Neurol, full length article	Melbourne, Australia	26	2.5 – 34.4 years (median 9.1)	15/11	Clinical	Video analysis	Clinical examination, FMS, radiography	****
Rilstone	2012	Epilepsia, full length article	Toronto, Canada	10	18 – 47 years (median 24.5)	4/6	Genetic	Clinical observation	Clinical examination, genetic screening, seizure counts	***
Fasano	2014	Neurology, short communication	Toronto, Canada	12	20 – 43 years (median 24.5)	4/8	Genetic	Video analysis	Clinical examination, mUPDRS	****
Gitiaux	2016	Neurology, full length article	Paris, France	12	2 – 17 years (median 7.5)	8/4	Genetic	Clinical observation	Clinical examination, NCS, needle EMG	**
Spagnolo	2016	Gait & Posture, conference abstract	Padua, Italy	19	Mean 12.8	Not reported	Genetic	Video analysis	WeeFIM	***
Hallemans	2016	Gait & Posture, conference abstract	Antwerp, Belgium	13	Mean 8.11, SD 2.1 years	6/7	Clinical	3D gait analysis	Clinical examination	****
Aljaafari	2017	Epilepsia, short communication	Toronto, Canada	14	20 – 46 years (median 27.5)	5/9	Genetic	Clinical observation	Clinical examination, mUPDRS	***
Wyers	2017	Gait & Posture, conference abstract	Antwerp, Belgium	16	3 – 22 years (mean 12.4)	Not reported	Not reported	3D gait analysis	Clinical examination	***
Verheyen	2018	Gait & Posture, conference abstract	Antwerp, Belgium	29	3 – 24 years (mean 13.3)	Not reported	Not reported	3D gait analysis	Clinical examination	***

m = male, f = female, 2D = two dimensional, 3D = three dimensional, FMS = Functional Mobility Scale, mUPDRS = modified Unified Parkinsons's Disease Rating Scale, NCS = nerve conduction study, EMG = electromyography, WeeFIM = Functional Independence Measures for Children, * stars earned on the adapted Newcastle-Ottawa quality assessment Scale

Table 3
Deviations in gait kinematics

	Sagittal plane				**Coronal Plane**				**Transverse Plane**		
			Dravet	**TD**			**Dravet**	**TD**		**Dravet**	**TD**
Kinematic parameters:	Hip flexion	IC	42° ± 8°	37° ± 2°	Hip adduction	MSt	9° ± 2°	7° ± 2°	Pelvis internal rotation	9° ± 3°	4° ± 2°
Significantly different joint (peak) angles (α = 0.05) (Hallemans et al., 2016)		Sw	44° ± 8°	36° ± 2°					Hip external rotation	18° ± 13°	-14° ± 12°
	Knee flexion	IC	15° ± 10°	8° ± 7°							
		LR	31° ± 7°	19° ± 3°							
		Sw	64° ± 8°	60° ± 3°							
	Ankle dorsiflexion	MSt	18° ± 3°	11° ± 3°							
		TSt	3° ± 5°	-17° ± 10°							
Kinematic time profiles:	Hip flexion		ca. 40 – 60%GC						Ankle external rotation	ca. 0 – 100 %GC	
Significantly different phases of the gait cycle (α = 0.05) (Wyers et al., 2017)	Knee flexion		ca. 30 – 50 %GC								
	Ankle dorsiflexion		ca. 55 – 70 %GC								
Gait Profile Scores: scores exceeding 2SD of TD (Verheyen et al., 2018)	4/29 patients (14%)				5/29 patients (17%)				15/29 patients (51%)		
	Total score: 13/29 patients (45%)										

TD = typically developing children, IC = initial contact, MSt = midstance, Sw = swing, LR = loading response, TSt = terminal stance, %GC = percentage of the gait cycle, SD = standard deviation

4.4.4 Musculoskeletal integrity

Physical examination for passive joint range of motion and skeletal alignment was performed in five studies (Gitiaux et al. 2016; Hallemans et al. 2016; Rodda et al. 2012; Verheyen et al. 2018; Wyers et al. 2017) and radiographs were taken to detect foot deformities in one (Rodda et al. 2012).

Three authors reported passive knee extension deficits in a minority of the patients (Gitiaux et al. 2016; Rodda et al. 2012; Wyers et al. 2017). 'Flessum of the knees' was observed by Gitiaux et al. (2016) in three out of twelve patients (Gitiaux et al. 2016) and mild hamstrings shortening by Wyers et al. (2017) with popliteal angles between 50° and 70° short to full extension in six out of fifteen patients (Wyers et al. 2017). In the study of Rodda et al. (2012), passive knee extension angles decreased and popliteal angles increased with increasing age. Mean angles in the oldest age group (adolescents, age ≥13) revealed only mild deficits (knee extension -2±7°, popliteal angle 35±14° short to full extension) (Rodda et al. 2012).

Indications for hypermobility were documented as 'ligamentous laxity' in six out of twenty-six patients (Rodda et al. 2012), 'hyperlaxity' in one out of twelve patients (Gitiaux et al. 2016) and excessive passive ankle dorsal flexion (≥25°, knee 90°) in nine out of sixteen patients (Wyers et al. 2017). Passive ankle dorsiflexion angles were higher (age 0-5y: mean 39±9°; age 6-12y: mean 32±7°, knee 90°) in younger children compared to adolescents (mean 22±10°, knee 90°) (Rodda et al. 2012).

Femoral anteversion was only slightly increased in three studies with values up to 30 degrees (Hallemans et al. 2016; Rodda et al. 2012; Wyers et al. 2017). Other malalignments consisted of external tibial torsion (bimalleolar axis of 31±7° in the ≥13 years subgroup) (Rodda et al. 2012) and pes planovalgus (eight times greater odds in patients aged 13 years and older (Rodda et al. 2012), pes valgus in three out of twelve patients (Gitiaux et al. 2016) and pes planovalgus in thirteen out of sixteen patients (Wyers et al. 2017). Femoral anteversion and tibial torsion did not correlate with the severity of the gait deviations in the transverse plane (Verheyen et al. 2018).

Three lateral radiographical parameters in the ≥13 years age group were larger than one standard deviation above the mean of normal references and significantly increased in older compared to younger children ($p<0.05$). These parameters were hindfoot abductovalgus (mean talocalcaneal angles 61±8°, compared to normative values 49±6.9°), midfoot pronation (mean naviculocuboid overlap angle 80±12°, norm 47±13.8°) and forefoot planus (mean talo-first metatarsal angle 35±8°, norm 13±7.5°) (Davids, Gibson, and Pugh 2005; Rodda et al. 2012).

Muscle strength measurements were not reported in the included studies. Moreover, three authors stated that muscle testing was not possible due to reduced cooperation or cognitive abilities of their participants (Fasano et al. 2014; Rilstone et al. 2012; Rodda et al. 2012).

4.4.5 Neurological signs

Neurological examination was discussed in five articles (Aljaafari et al. 2017; Fasano et al. 2014; Gitiaux et al. 2016; Rilstone et al. 2012; Rodda et al. 2012). Spasticity was only present in four cases out of the fourteen patients from Toronto (Aljaafari et al. 2017; Fasano et al. 2014; Rilstone et al. 2012) and not observed in other studies (Gitiaux et al. 2016; Rodda et al. 2012). Cerebellar dysfunction was assessed in two studies. Although no patients had gait ataxia in the study of Rilstone et al. (2012), they did show cerebellar signs such as dysarthria in six out of ten and intentional tremor in four out of ten adult patients (Rilstone et al. 2012). Gitiaux et al. (2014) on the contrary did not observe tremor, adiadochokinesia or dysmetria, but reported ataxia without specification in five out of ten younger patients (Gitiaux et al. 2016).

Parkinsonism was investigated in the study group from Toronto using a modified Unified Parkinson's Disease Rating Scale (mUPDRS, score between 0 and 76, higher values indicating more severe parkinsonism) with scores between 0 and 25 as a result, significantly correlated with age ($\rho = 0.61$, $p = 0.03$) (Aljaafari et al. 2017; Fasano et al. 2014). Parkinsonian features such as antecollis, bradykinesia and cogwheel rigidity were present in at least eleven of their fourteen cases (Aljaafari et al. 2017; Fasano et al. 2014). Rodda et al. (2012) did not use a Parkinson rating scale, but noted postural kyphosis as part of the crouch gait posture in adolescents and young adults (Rodda et al. 2012). Gitiaux et al. (2014) on the other hand stated that none of the patients presented with extrapyramidal signs (Gitiaux et al. 2016). Two patients received levodopa treatment and experienced improvement in slowness and rigidity (Fasano et al. 2014). When compared to Lennox-Gastaut syndrome, parkinsonian gait was significantly more present, but no significant difference in the severity of parkinsonism features was found (Aljaafari et al. 2017; Fasano et al. 2014).

4.4.6 Activities and participation

At the level of activities and participation, Rodda et al. (2012) observed a large variation in scores on the Functional Mobility Scale (FMS) for walking distances over 500m in adolescents and adults, with four patients leaning on others and one patient using a wheelchair. The Gillette Functional Assessment Questionnaire did not reveal any significant difference between age groups (Rodda et al. 2012). Out of the five patients who walked in

crouch in the study of Rilstone et al. (2012), three needed support to walk distances over 50m and two were not able to walk more than short distances of 5m, necessitating the use of a wheelchair outside the home (Rilstone et al. 2012). The mean total score on the Functional Independence Measures for Children (WeeFIM) in the study of Spagnolo et al. (2016) was 93 on a maximum of 126, indicating decreased independence (Spagnolo et al. 2016).

5. Discussion

The aim of this literature review was to establish the state of the art regarding the evaluation of gait deviations in patients with Dravet Syndrome. Although research on this subject is scarce, this systematic review in four databases provides an overview of peer reviewed articles and conference abstracts. Small sample sizes and large heterogeneity in patient ages and measurement methods make it difficult to draw a general conclusion. Wide age ranges in the included studies make it hard to separate stable features of the syndrome from age-dependent characteristics.

The most reported gait pattern was crouch gait, observed by the majority of authors in about half of the population. Crouch is a sagittal plane pattern defined as excessive ankle dorsiflexion with excessive hip and knee flexion during stance phase and is common in patients with spastic diplegic cerebral palsy (Rodda et al. 2004). The cause of crouch gait is multifactorial and may include muscle weakness, spasticity, contractures or lever arm dysfunction (Kedem and Scher 2016). Clinical examination findings on these factors were inconsistent in patients with Dravet Syndrome. Moreover, testing muscle strength is especially difficult due to low cognitive or behavioural capacities. Further investigation of muscle strength and bony deformities is needed to document possible causes of crouch gait in this population.

Large standard deviations around the mean kinematics in the studies of Hallemans et al. (2016) and Wyers et al. (2017) suggested differences in severity of deviations, with part of the observations situated within the normal range (Hallemans et al. 2016; Wyers et al. 2017). Furthermore, not only knee joint motion in the sagittal plane, but also ankle joint and transverse plane deviations should be evaluated in patients with Dravet Syndrome (Hallemans et al. 2016; Spagnolo et al. 2016; Verheyen et al. 2018; Wyers et al. 2017).

Other observed patterns include parkinsonian and cerebellar gait, but no specification of

this classification was provided (Aljaafari et al. 2017). Characteristics of parkinsonism such as levodopa responsive bradykinesia, shuffling gait, rigidity and trunk anteflexion were inconsistently described in mostly adult populations (Aljaafari et al. 2017; Fasano et al. 2014; Rodda et al. 2012). The observation of cerebellar signs or ataxia in patients with Dravet Syndrome is controversial. Depending on how authors define ataxia, different conclusions have been reported (Ceulemans and Cras 2004; Dravet 2011; Gitiaux et al. 2016; Rilstone et al. 2012; Scheffer 2012). Ataxia-like clumsiness in toddlers lasts longer than expected (Scheffer 2012), which explains why ataxia was only observed in young children by one author (Gitiaux et al. 2016). Other findings on cerebellar symptoms were contradictory (Aljaafari et al. 2017; Gitiaux et al. 2016; Rilstone et al. 2012). Ataxia may temporarily appear after prolonged seizures and later become a constant part of a patient's motor problems (Ceulemans and Cras 2004; Dravet 2011). It remains unclear whether true cerebellar ataxia is present in patients with Dravet Syndrome (Scheffer 2012). The large variety and lack of specification in terminology illustrates how difficult it is to formulate an accurate description of the gait pattern in patients with Dravet Syndrome.

It is not well understood how the gait deviations evolve from childhood to adulthood. Studies on children and adolescents focussed on deviations in joint range and alignment (Hallemans et al. 2016; Rodda et al. 2012; Spagnolo et al. 2016; Verheyen et al. 2018; Wyers et al. 2017), while in adult patients merely neurological aspects of gait were assessed (Aljaafari et al. 2017; Fasano et al. 2014; Rilstone et al. 2012). A combination of all observations suggests that children younger than six years of age have a normal or variable gait pattern with possibly features of joint hypermobility and ataxia (Gitiaux et al. 2016; Rodda et al. 2012). By adolescence (age ≥ 13), part of the patients have developed a flexed gait pattern with passive knee extension deficit and bony malalignment (Rodda et al. 2012). In adulthood, parkinsonian gait and extrapyramidal signs become evident (Aljaafari et al. 2017; Fasano et al. 2014). Other neurological signs such as spasticity, dysarthria and intentional tremor are infrequently observed (Aljaafari et al. 2017; Rilstone et al. 2012). These observations can only cautiously be interpreted as an evolution in the gait deviations, since they are based on cross-sectional studies. Longitudinal studies are needed to document the evolution of gait in patients growing older.

Although the gait patterns may resemble those of patients with cerebral palsy, Parkinson's disease or cerebellar dysfunction, the pathophysiology in Dravet Syndrome is different and should be approached as such. Dravet Syndrome is primarily caused by loss-of-function mutations in the *SCN1A*-gene that encodes the voltage-gated sodium channel type-1 ($Na_v1.1$)

largely distributed in the central nerve system (Dravet 2011). Reduced function of GABAergic interneurons results in an imbalance of excitatory over inhibitory neurotransmission which causes epilepsy and co-morbidities (Catterall 2018). Depending on the site or structure where the $Na_v1.1$ channels are expressed, different aspects of movement disorders are induced. Motor neuron dysfunction could partially explain the gait features with at first distal mild motor deficits followed by proximal (crouch-like) deficits (Gitiaux et al. 2016). Involvement of basal ganglia dysfunction on the other hand could explain levodopa responsive parkinsonism symptoms (Fasano et al. 2014). The vulnerability of the dopaminergic system to ageing (Rothera et al. 2002) explains why parkinsonism was only described in adult populations, where it showed a clear correlation with age (Fasano et al. 2014). Deficits in cerebellar Purkinje neurons might cause ataxia (Kalume et al. 2007), but evidence for this mechanism in humans is lacking (Catterall 2018). To understand the gait problems, we should think of Dravet Syndrome as a sodium channel interneuronopathy causing complex clinical presentations of varying nature.

The independence of a person with Dravet Syndrome is decreased, not only because of cognitive disabilities, but also due to walking difficulties. At least 15% to 30% of the patients need support from a person to walk outside the house and up to 20% use a wheelchair (Rilstone et al. 2012; Rodda et al. 2012). The use of walking aids was not reported in this population. Clinicians should recognise the impact of the motor problems on daily activities and participation in society and address them with appropriate interventions. Treatment could include orthopaedic management of foot deformities and targeted physiotherapy programs, but evidence regarding intervention outcomes is lacking. The decision-making process should be guided by appropriate gait evaluation (Wren et al. 2011).

Most descriptions of gait deviations were based on clinical observation or video analysis. The reliability of these methods highly depends on the experience of the assessor (Viehweger et al. 2010) and their results should be considered as subjective and qualitative descriptions of the gait pattern. Instrumented 3D gait analysis on the other hand is an objective and quantitative measurement tool. It is standard procedure in the treatment of patients with cerebral palsy where it adds an important value to clinical decision making (Desloovere et al. 2006). However, its use in patients with Dravet Syndrome was only briefly documented in conference abstracts of the same research group and not reported in peer reviewed articles. Further research on kinematics of gait is needed for more profound documentation of the gait problems. There are currently no studies published on kinetics and electromyography during gait in this population. These aspects however are essential for better understanding

of the underlying mechanism of pathological gait as they enable an integrated analysis of lever arm function and muscle activity covering the link between clinical examination findings and kinematic abnormalities (Gage 1993).

An explanation for the lack of 3D gait analysis studies in this population is the challenge of the assessment protocol itself. The complete assessment takes about two hours and is not only physically tiring, but also requires good cooperation of the participant (Baker et al. 2016). Not all patients are able to comply with the test requirements because of cognitive or behavioural difficulties and thus appropriate data are hard to collect. Alternative methods exist that are more user friendly such as video gait assessment tools (Rathinam et al. 2014), inertial sensors (Petraglia et al. 2018) or electronic walkways (Wondra, Pitetti, and Beets 2007). Future research is desirable to elaborate gait analysis protocols that offer standardized and reliable measurements but are also easily applicable in patients with Dravet Syndrome and other patients with intellectual disabilities or behavioural problems.

The inclusion of conference abstracts in this review implied a weakness because they contain limited information on methods and results and are not peer reviewed. On the other hand, in the largely understudied area of this subject, inclusion of conference abstracts offered a more complete overview of the investigations that were performed. Two patient cohorts reappear in three studies each. These studies do not necessarily add new data but a different perspective on the same patients. Therefore the observations of Rilstone et al. (Rilstone et al. 2012), Fasano et al. (Fasano et al. 2014) and Aljaafari et al. (Aljaafari et al. 2017) and the kinematic data from Hallemans et al. (Hallemans et al. 2016), Wyers et al. (Wyers et al. 2017) and Verheyen et al. (Verheyen et al. 2018) should not be accumulated to avoid overrepresentation of the same patients. Another limitation of this review was the moderate to low methodological quality of the included studies. Risk of bias was increased due to not mentioning the diagnostic criteria in two studies (Verheyen et al. 2018; Wyers et al. 2017), less repeatable outcome assessments in two other studies (Aljaafari et al. 2017; Gitiaux et al. 2016) and lack of statistical tests in three studies (Gitiaux et al. 2016; Rilstone et al. 2012; Spagnolo et al. 2016).

6. Conclusion

This systematic review found evidence for the existence of a large variety of gait deviations in patients with Dravet Syndrome. A subgroup of patients seems to exhibit a crouch gait pattern, although possible causes such as muscle weakness, spasticity or contractures are rarely documented. The causal mechanism and pathophysiology of the gait deviations is still insufficiently understood. Progressive deterioration of gait, joint range and alignment and neurological signs is hypothesised and should be further investigated in longitudinal research. Clinicians should pay attention to evaluation and treatment of gait disorders in order to improve the patients' functional independence. Future research should ideally proceed with 3D gait analysis including kinetics and electromyography for increased insight in gait pathology. However, gait analysis protocols that are feasible and achievable in daily clinical practice need to be developed as well.

7. Study funding

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Appendix

Newcastle - Ottawa quality assesment scale adapted for cross-sectional studies

First Author	Year	Selection items			Outcome items		Total number of stars
		1	2	3	1	2	
Rodda	2012	A*	B	B*	B*	A*	4
Rilstone	2012	B*	B	A*	B*	B	3
Fasano	2014	A*	B	A*	B*	A*	4
Gitiaux	2016	A*	B	A*	C	B	2
Spagnolo	2016	B*	B	A*	B*	B	3
Hallemans	2016	B*	B	B*	A*	A*	4
Aljaafari	2017	B*	B	A*	C	A*	3
Wyers	2017	B*	B	C	A*	A*	3
Verheyen	2018	B*	B	C	A*	A*	3

Note: A maximum of one star can be earned per item with a total of five stars. The item 'Comparability' from the original NOS was not applicable in this study, because a comparison group was not required.

Selection

1) Representativeness of the sample

a) truly representative of the average in the community (random sampling or consecutive cohort) *

b) somewhat representative of the average in the community (non-random sampling) *

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Sample size

a) justified and satisfactory (sample size calculations reported) *

b) not justified

3) Ascertainment of exposure (diagnosis)

a) genetical *

b) clinical *

c) no description

Outcome

1) Assessment of outcome (gait evaluation)

a) three dimensional gait analysis *

b) video gait analysis *

c) clinical observation

d) no description or other (parent report)

2) Statistical test

a) the statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals or the probability level (p-value) *

b) the statistical test is not appropriate, not described or incomplete

Chapter 3

The mechanics behind gait problems in patients with Dravet Syndrome

Chapter 3

The mechanics behind gait problems in patients with Dravet Syndrome

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1. Abstract

Background: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy starting in infancy and characterised by treatment resistant epilepsy with cognitive impairment and progressive motor dysfunction. Walking becomes markedly impaired with age, but the mechanical nature of gait problems remains unclear.

Research question: What are the kinetic strategies characterised in gait of patients with DS?

Methods: This case-control study compared 41 patients with DS aged 5.2 to 26.1 years (19 female, 22 male) to 41 typically developing (TD) peers. Three dimensional gait analysis (VICON) was performed to obtain spatiotemporal parameters, kinematics and kinetics during barefoot, level walking at self-selected walking velocity. The sagittal plane support moment was analysed using Statistical Parametric Mapping (SPM). Three DS subgroups were identified based on differences in kinetic strategies characterised by the net internal knee joint moments and trunk lean. Kinematic and kinetic time profiles of the subgroups were compared to the TD group (SPM t-test). Clinical characteristics from physical examination and parental anamnesis were compared between DS (sub)groups using non-parametric tests (Kruskal-Wallis, Wilcoxon rank-sum, Fisher's exact).

Results: Support moments in stance were significantly increased in the DS group compared to TD and strongly related to minimum knee flexion in midstance. Persistent internal knee extension moments during stance were detected in a subgroup of 27% of the patients. A second subgroup of 34% showed forward trunk lean and attained internal knee flexion moments. The remaining 39% had neutral or backward trunk lean with internal knee flexion moments. Subgroups differed significantly in age and functional mobility.

Significance: Inefficient kinetic patterns suggested that increased muscle effort was needed to control lower limb stability. Three distinct kinetic strategies that underly kinematic deviations were identified. Clinical evaluation of gait should pay attention to knee angles, trunk lean and support moments.

2. Introduction

Dravet Syndrome (DS) is a developmental and epileptic encephalopathy characterized by drug resistant infantile onset seizures with cognitive and progressive motor impairments (Dravet 2011; Scheffer et al. 2017). It is primarily caused by mutations in the neuronal sodium voltage-gated channel type 1 alpha subunit encoding gene (*SCN1A*) (Claes et al. 2001). The sodium channel interneuronopathy induces intractable epileptic seizures and a variety of comorbidities (Catterall 2018). Around adolescence, walking problems become evident, making many of the patients lean on others or use a wheelchair for longer distances (Rodda et al. 2012). Literature on gait deviations in patients with DS is still scarce and mainly observational (Wyers, Van de Walle, Hoornweg, et al. 2019). Quantitative analysis of gait in this population is only recently reported (Di Marco et al. 2019). Crouch gait is often described in about half of the population, next to a variety of other deviations (Wyers, Van de Walle, Hoornweg, et al. 2019; Di Marco et al. 2019). Crouch gait is defined by excessive knee flexion in stance and was originally described in populations with cerebral palsy, where it is caused by a complex of muscle weakness, spasticity and contractures (Sutherland and Davids 1993; Rodda et al. 2004). However, these symptoms are rarely seen in patients with DS (Brunklaus et al. 2012; Wyers, Van de Walle, Hoornweg, et al. 2019), hence the nature of their gait problems remains unclear.

Studying biomechanics provides insight in how the central nervous system controls movements. The central nervous system can select many combinations of muscle forces to yield the same moment around a joint. Moreover, many combinations of hip, knee and ankle moments can result in the same knee angle. Therefore, when deviations in joint angles (kinematics) are observed, analysis of muscle and soft tissue forces that cause these motions (kinetics) is necessary to understand the neuromuscular control behind gait abnormalities (Winter and Eng 1995).

To obtain an indicator of lower limb control during gait (Winter 1980; Hof 2000), Winter (1980) proposed to combine the three major lower limb moments into one single measure: the 'support moment' (M_S), defined as the algebraic sum of the net internal extension moments at hip, knee and ankle (Winter 1980). The magnitude of the M_S depends on the ground reaction force (GRF) and the knee flexion angle and can be interpreted as the total internal extension moment that is generated to prevent collapse of the stance limb (Hof 2000). Relatively higher MS may thus suggest that extensor muscles are inducing larger moments and more muscular effort is needed to stabilise the limb.

To maintain stability of the stance limb in normal gait, ankle plantar flexors are active in midstance to slow down the forward momentum and align the GRF anterior to the knee. An internal hip and knee flexion moment produced by soft tissue forces is attained during single leg stance. This way, less muscle activity is required, which optimizes the energy expenditure (Gage 1993). When a person fails to align the GRF in front of the knee, persistent internal knee extension moments occur, greatly increasing energy demands (Gage 1993). Forward trunk lean influences the direction of the GRF and is often observed as a compensatory strategy to reduce this internal extension moment (Heyrman et al. 2014).

The observed gait deviations in patients with DS, especially wide based and crouch gait, may reflect a lack of stance limb stability (Di Marco et al. 2019), probably caused by underlying neuromuscular control disturbance (Gitiaux et al. 2016; Catterall 2018; Aljaafari et al. 2017). Recently, Di Marco et al. (2019) reported gait kinematics of patients with DS (Di Marco et al. 2019), but to our knowledge, no studies on gait kinetics in DS have been published yet. Therefore, this study aims to characterise kinetic strategies employed by patients with DS to support the lower limb during stance phase of gait. First, analysis of the MS may provide evidence of lower limb support abnormalities. Furthermore, distinguishing subgroups based on differences in kinetic strategies characterised by the net internal knee joint moments and trunk lean, may enhance understanding of the heterogeneity of gait deviations. Lastly, detecting differences in gait and clinical characteristics between these subgroups may highlight the functional impact of the observed kinetic strategies.

3. Methods

3.1 Study design and setting

This case-control study was part of a larger project registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03857451) and approved by the ethics committees of the Antwerp and Leuven University Hospitals (Belgian Registration Number: B300201627079). Patient data collection was performed between May 2016 and February 2020 (most recent session selected per patient) at the Multidisciplinary Motor Centre Antwerp (M²OCEAN).

3.2 Participants

Volunteers with DS were recruited through the department of child neurology at the Antwerp University Hospital and the parent organization of the Netherlands and Flanders 'Stichting

Dravetsyndroom Nederland/Vlaanderen'. All candidates with a clinical diagnosis with DS were included if *SCN1A* mutation was confirmed and they had a minimum age of five and maximum of 25 years at enrolment. Exclusion criteria were the occurrence of a severe epileptic seizure within 24 hours before assessment and comorbidities of neurological and/or orthopaedic disorders not related to DS (figure 1).

3.3 Data collection

3.3.1 Gait data

Body segment motion and ground reaction forces were captured and processed using a VICON system (Nexus v2.8.1, VICON, Oxford Metrics, Oxford, UK) with eight optoelectronic cameras (100 Hz), two optical cameras (50 fps, Basler AG, Ahrensburg, Germany) and four force plates (1000 Hz, low-pass filtered at 20 Hz, AMTI, Watertown, MA, US). Retroreflective markers were placed following the PlugInGait Lower Limb marker model (Davis et al. 1991). All participants performed walking trials at self-selected walking velocity. Patients were only included when kinetic data were successfully collected. A control group, balanced for age, was selected from available databases of typically developing children and healthy adults without neurological or orthopaedic conditions, collected at M²OCEAN and the Clinical Motion Analysis Laboratory of the University Hospital Pellenberg, Leuven (CMAL-P), collected and processed with identical procedures. All gait analysis and physical examination data were collected by the same two researchers (L.W. and K.V., MSc physiotherapists)

3.3.2 Clinical characteristics

Via medical record screening and parental anamnesis, the following information was obtained: type of mutation, age of epilepsy onset, current epileptic severity and age of independent walking. The patients usual mobility was inquired using the Functional Mobility Scale (FMS) and by asking the maximum distance the patient was currently able to walk ('walking distance'). Note that we gave FMS score four when the patient usually held a person's hand (Graham et al. 2004). Levels of intellectual disability (ID) were estimated as mild, moderate or severe, supported by cognitive test scores if available (Greenspan and Woods 2014). During physical examination, goniometric measures of joint range of motion (RoM), muscle length and skeletal alignment were obtained and compared to age-related norm values (Mudge et al. 2014; Redmond, Crane, and Menz 2008).

3.4 Data processing

Spatiotemporal parameters, lower limb joint kinematics and kinetics were calculated. Visual inspection of data quality and further processing was performed using custom made MATLAB® software (vR2018a, The Mathworks Inc, Natick, MA, US). Spatiotemporal and kinetic data were non-dimensionally normalized for leg length, body mass and gravitational acceleration (Hof 1996; Pinzone, Schwartz, and Baker 2016). For each instant of the gait cycle, sagittal plane MS were calculated according to the formula by Hof (2000) (Hof 2000).

$$M_S = M_H/2 + M_K + M_A/2$$

with M_H, M_K, and M_A indicating the net internal moment (positive values for extension) around hip, knee and ankle respectively (Hof 2000). Per participant, all available trials of one randomly selected side (ranging from one to twelve trials) were averaged, because further analyses required single observations per subject.

Trunk lean was assessed by one researcher (L.W.) based on sagittal plane video images. The angle between vertical and the trunk axis (estimated trochanter major to acromion) was measured on a still frame taken at 'opposite toe-off' using Kinovea (v0.8.15, http://www.kinovea.org). Trunk lean was then categorized as 'neutral' (between vertical and 5° of forward or backward inclination), 'forward' or 'backward' (Read et al. 2003; Heyrman et al. 2014).

3.5 Subgrouping

We constructed a decision making tree to identify subgroups within DS based on minimal sagittal knee moment in midstance (between 30% of stance phase and toe-off) and trunk lean. The KMext subgroup was defined by a persistent internal knee extension moment throughout stance, regardless of trunk position. The KMflex-Tf subgroup contained patients who attained an internal knee flexion moment in midstance in combination with forward trunk lean. The remaining patients formed the KMflex-Tn/b subgroup, characterized by an internal knee flexion moment in combination with a neutral or backward inclined trunk (figure 1).

3.6 Statistical analysis

Spatiotemporal parameters and clinical characteristics were analysed using non-parametric tests, since graphical inspection and formal tests (Kolmogorov-Smirnov) revealed that the assumption of normality was not fulfilled. Wilcoxon rank-sum tests (two-tailed α=.05) were used to compare age, BMI and non-dimensional spatiotemporal parameters between DS

and TD. Fisher's exact tests (categorical data, including physical examination categorised as 'normal' or 'deviant') and Kruskal-Wallis tests (two-tailed, α=.05) with post-hoc pairwise Wilcoxon rank-sum tests with Bonferroni correction (numerical data) were used to identify differences in clinical characteristics between subgroups. As Fisher's exact test is somewhat conservative (Lydersen et al. 2007), α-levels were set at 0.10 for this test.

Kinematic and kinetic time profiles were analysed using statistical parametric mapping (SPM) (Pataky, Robinson, and Vanrenterghem 2013). Prior to SPM analyses, time profiles were normalized to 50% stance and 50% swing phase, in order to eliminate influence of differences in stance phase duration. Test statistics (*t*-test or regression, see further) were calculated for each time node and expressed as SPM*{t}* trajectories. A critical threshold was then defined that only 5% (α=0.05) of identically smooth random curves were expected to exceed. Parts of the gait cycle where SPM*{t}* trajectory crossed this threshold were identified as clusters with significant outcome, for which cluster-specific P-values were calculated based on the Random Field Theory (Pataky 2010). Small clusters (<3% GC) were not considered clinically relevant and therefore not discussed. An SPM *t*-test was used to identify differences in M_S between DS and TD. SPM regression analyses explored association with walking velocity and minimum knee angle in midstance for DS and TD separately. After that, SPM *t*-tests were used to detect kinematic and kinetic deviations comparing each subgroup to the TD group. Bonferroni correction for multiple testing brought α to .017. All SPM analyses were performed using spm1d open source code (vM.0.4.5, http://www.spm1d.org) in MATLAB®. All other statistical analyses were executed in R (v4.0.0, R Foundation, Vienna, Austria).

4. Results

4.1 Participants

Out of 50 candidates, 41 patients aged 5.2 to 26.1 years (19 female, 22 male) were included in this study (individual characteristics: appendix, table A1). Five patients were not eligible and four others were not cooperative enough to collect kinetic data (figure 1). The control group of 41 TD individuals did not differ from the DS group for age and BMI. Participants with DS walked significantly slower with shorter and wider steps and longer relative stance time (*P*<.05; table 1).

4.2 Support moment

SPM *t*-test showed a significantly higher M_S (*P*<.001) in the DS group during most of stance phase (figure 2, left panel). Significant positive associations between M_S and walking velocity were identified in early stance (*P*<.001) only for the DS group. Significant positive associations (*P*<.001) with minimum knee flexion angle in midstance were observed for the majority of stance for both groups (figure 2, middle panel). The absence of an association with walking velocity in midstance and the significant correlation with knee angle are illustrated for one time point (50% stance phase) in figure 2, right panel. Details of SPM analyses can be consulted in appendix figure A1.

4.3 Subgrouping

Three DS subgroups were identified using the decision making tree. The *KMext subgroup* included eleven patients (27%) of whom five walked with neutral trunk and six showed forward lean. The *KMflex-Tf subgroup* consisted of fourteen patients (34%). The *KMflex-Tn/b subgroup* of sixteen patients (39%) of whom seven had a neutral trunk position and nine a backward lean (figure 1).

Table 1

Comparison of patient and control group

	DS (n = 41)	**TD (n = 41)**	***P*-value**
	median (IQR)	**median (IQR)**	**Wilcoxon**
Demographics:			
Age (years)	11.4 (10.1)	12.0 (9.1)	0.98
Gender (f / m)	19 / 22	27 / 14	
BMI	17.0 (8.6)	17.1 (5.4)	0.68
Spatiotemporal parameters:			
Walking velocity (m/sec)	1.03 (0.37)	1.21 (0.20)	
Non-dimensional walking velocity	0.360 (0.136)	0.460 (0.082)	<0.001*
Cadence (steps/sec)	2.01 (0.45)	2.02 (0.33)	
Non-dimensional cadence	0.570 (0.091)	0.560 (0.048)	0.71
Step length (m)	0.49 (0.18)	0.55 (0.15)	
Non-dimensional step length	0.650 (0.166)	0.760 (0.155)	0.006*
Step width (m)	0.16 (0.06)	0.10 (0.04)	
Non-dimensional step width	0.220 (0.096)	0.130 (0.061)	<0.001*
Stance time (%GC)	60.4 (4.4)	59.3 (2.5)	0.02*

Median and interquartile range (IQR) with *P*-value of the Wilcoxon rank-sum test. *Significant at α = 0.05; DS, Dravet Syndrome; TD, typically developing; f, female; m, male; BMI, Body Mass Index.

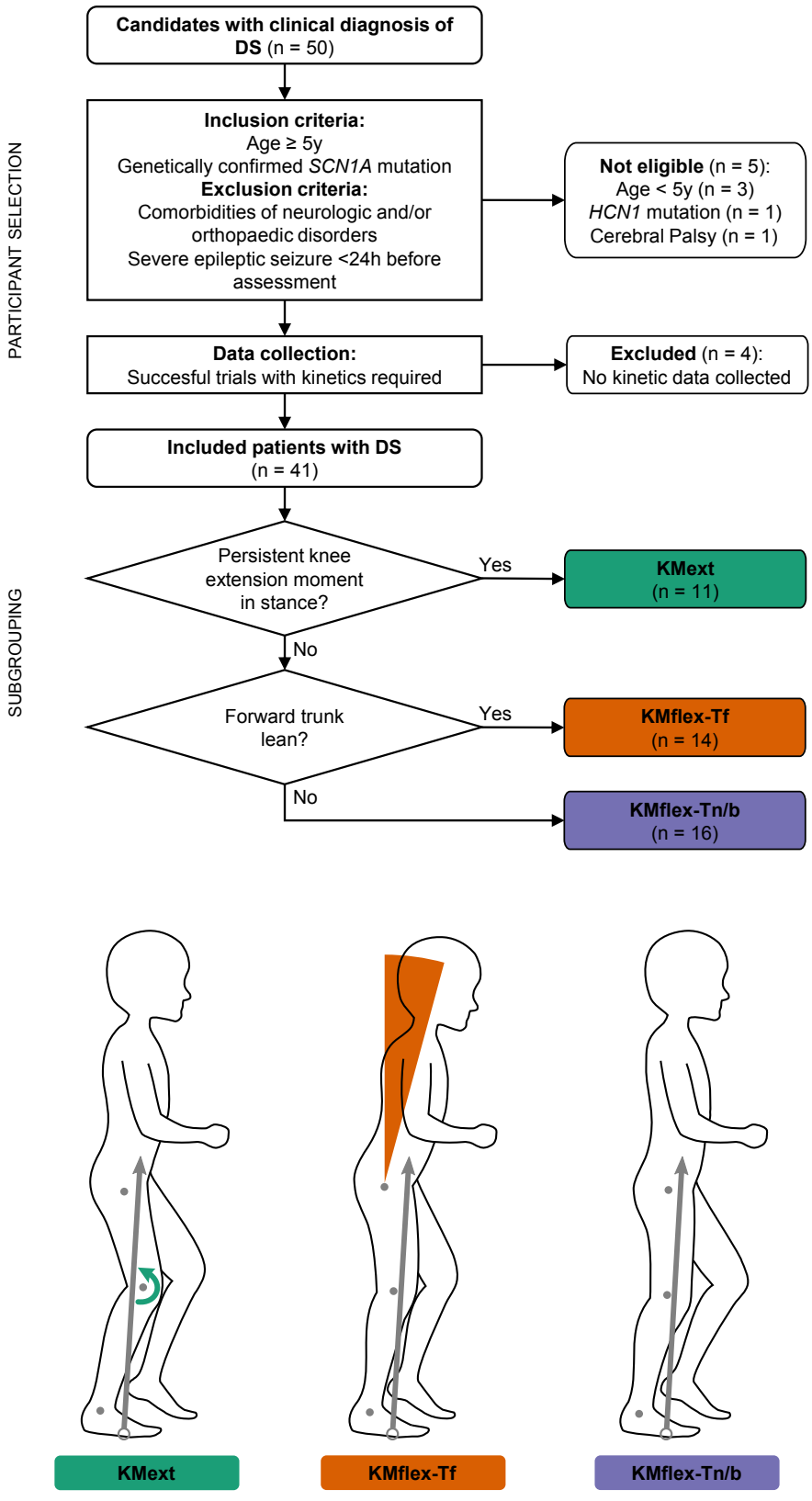

Figure 1. Illustrated flow chart of the participant selection and subgrouping process. Patients who fail to align the GRF (grey arrow) in front of the knee, show a persistent internal knee extension moment (green arrow). Forward trunk lean (>5°; orange angle) influences the direction of the GRF. DS, Dravet Syndrome; TD, Typically Developing; KM, internal knee moment flexion (flex) or extension (ext); T, trunk lean forward (f) neutral (n) or backward (b).

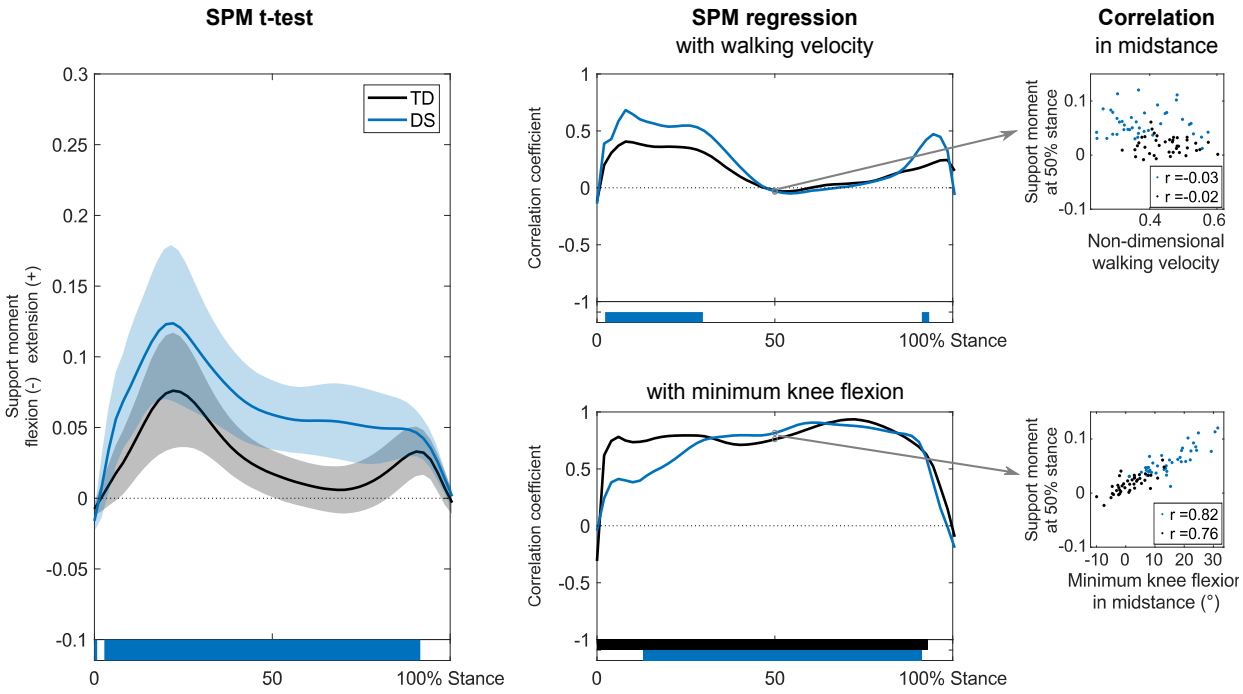

Figure 2. The support moment and its association with walking velocity and minimum knee flexion. Left: The non-dimensional support moment (averaged curve with 1SD region) was increased in patients with Dravet Syndrome (DS, blue) compared to typically developing participants (TD, black) Middle: Coefficients of the correlation between non-dimensional sagittal support moment and walking velocity (upper) and minimum knee flexion angle in midstance (lower). Right: In midstance, association with walking velocity was absent, but with minimum knee flexion was significant, as illustrated for 50% of stance phase. Horizontal bars represent clusters with significant differences (SPM t-test, left) or significant associations (SPM regression, middle).

4.4 Gait pattern

Comparison of kinematic and kinetic curves (internal moments) revealed significant differences for each subgroup compared to the TD group (figure 3).

In *KMext*, kinematics were characterized by significantly increased hip (*P*<.001) and knee (*P*<.001) flexion for most of the gait cycle, increased ankle dorsiflexion in mid- and terminal stance (MSt-TSt; *P*<.001), decreased ankle plantar flexion in initial swing (ISw; *P*=.004) and increased external foot progression (*P*<.001). The underlying M_S was significantly increased in loading response (LR; *P*=.001) and MSt-TSt (*P*<.001), resulting from decreased flexion moments at the hip in TSt (*P*<.001), increased knee extension moments in MSt-TSt (P<.001), ankle plantarflexion moments in LR (*P*=.001) and decreased plantarflexion moments around TSt (*P*<.001).

In *KMflex-Tf*, kinematics were characterized by increased anterior pelvic tilt (*P*<.001), hip (*P*<.001) and knee (*P*<.001) flexion over the entire gait cycle, with increased dorsiflexion in LR (*P*=.004) and MSt (*P*=.016) and decreased dorsiflexion in pre-swing (PSw) and ISw (*P*<.001) and increased external foot progression (*P*<.001). The M_S was significantly increased from LR to TSt (*P*<.001), resulting from increased hip extension moments in LR (*P*=.014) and MSt-TSt (*P*<.001), knee flexion moments in LR (*P*=.017) and TSt (*P*<.001) and plantarflexion moments in LR (*P*<.001) and decreased plantarflexion moment around TSt (*P*<.001). Furthermore, first (*P*=.002) and second (*P*<.001) peak hip abduction moment were decreased.

In *KMflex-Tn/b*, kinematics were characterized by increased hip flexion over stance and ISw (*P*<.001) and in terminal swing (TSw; *P*=.016) and knee flexion from initial contact to TSt (*P*<.001) and in TSw (*P*=.011) and increased external foot progression (*P*<.001). Ankle dorsiflexion was increased in LR (*P*=.006), MSt (*P*=.004), PSw (*P*=.012) and ISw (*P*<.001). Significantly increased M_S were found in LR (*P*=.002) and in MSt (*P*<.001), resulting from decreased hip flexion moments in TSt (*P*<.001), knee extension moments in LR (*P*=.012) and MSt-TSt (*P*<.001), and plantarflexion moments in TSt (*P*=.001). Furthermore, second peak hip abduction moment was decreased (*P*<.001).

In swing, significant differences in joint moments were also identified for each subgroup, but will not be discussed since they did not attribute to stance limb support. Additional graphs of coronal and transverse plane are reported in the appendix (figure A2). Details of SPM analyses can be consulted in the appendix, (figure A3).

4.5 Clinical characteristics

Subgroups differed significantly in age, walking distance and the FMS-500m scores. Post-hoc tests indicated that *KMext* contained older participants than *KMflex-Tf*, while patients in *KMflex-Tn/b* could walk longer distances and walked more independently (table 2). Abnormalities in RoM, muscle length and alignment were present in the three subgroups, equally distributed. Most frequent deviations were plantar flexor tightness, external tibial torsion and planovalgus feet (table 3). No clear spasticity was detected.

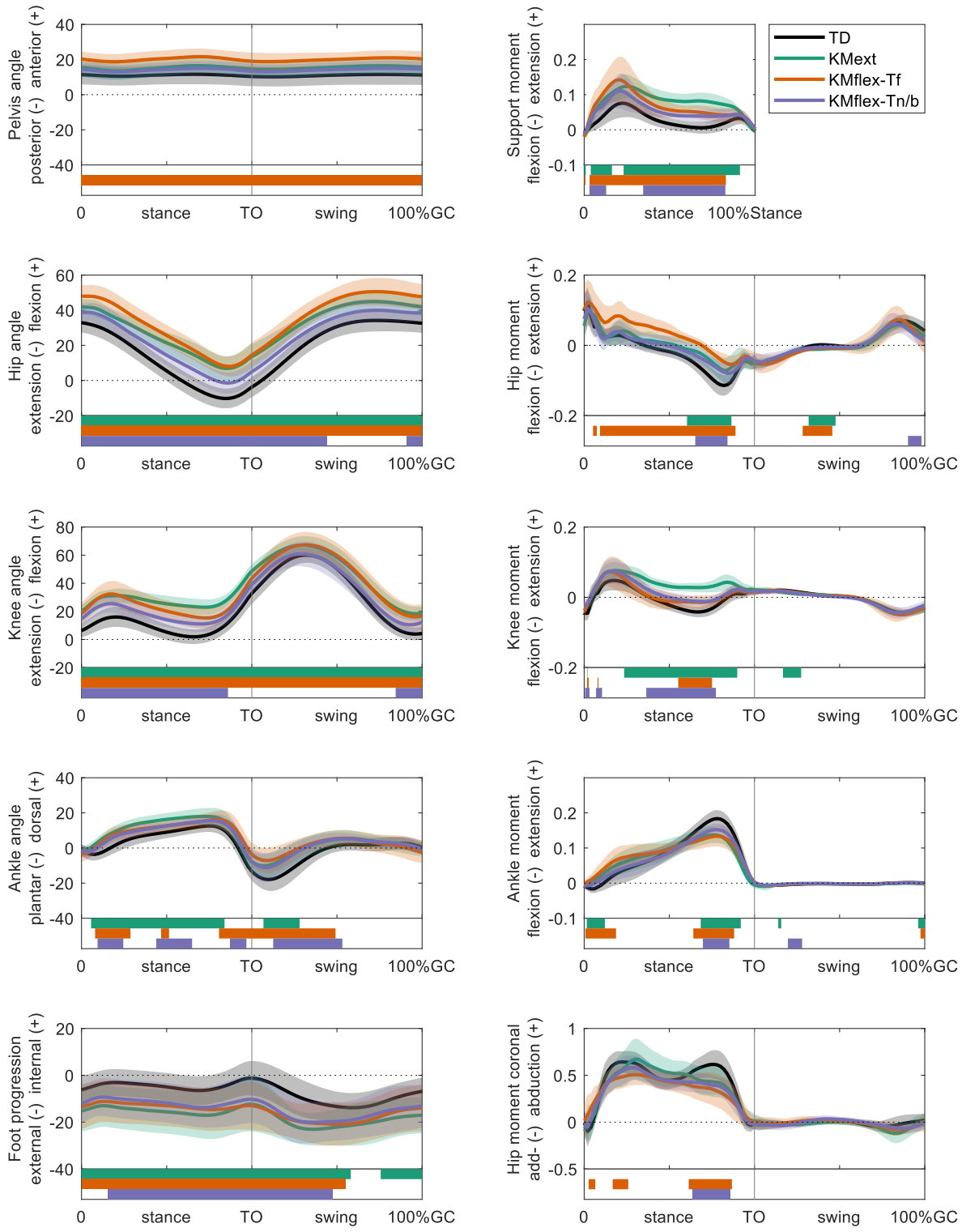

Figure 3. Comparison of kinematic and kinetic curves between Dravet Syndrome subgroups and typically developing (TD) controls. Group averaged curves and 1SD regions are plotted for joint angles (°) and internal net joint moments (non-dimensional) in the sagittal plane, complemented with the foot progression angle (under, left) and hip moment in the coronal plane (under, right). Horizontal bars represent clusters with significant differences (SPM t-tests) comparing subgroups with the TD group. TO, toe off; GC, gait cycle.

	KMext (n = 11)	KMflex-Tf (n = 14)	KMflex-Tn/b (n = 16)	*P*-value		
	median (IQR) or n (%)	median (IQR) or n (%)	median (IQR) or n (%)	K-W	Fisher	Post-hoc
Age (years)	17.1 (5.5)	9.2 (6.9)	11.1 (8.9)	0.04		0.03 (a)
Gender (f / m)	5 / 6	7 / 7	7 / 9			
BMI	19.2 (11.0)	17.1 (4.5)	16.1 (5.7)	0.45		
Age of onset epilepsy (months)	5 (4)	5 (4)	5 (2)	0.80		
Current epileptic frequency					0.17	
Free (for >1 year)	1 (9%)	3 (21%)	6 (38%)			
Mild (yearly)	5 (45%)	5 (43%)	4 (25%)			
Moderate (monthly)	0 (0%)	3 (21%)	4 (25%)			
Severe (weekly)	5 (45%)	2 (14%)	2 (13%)			
Intellectual disability:					0.42	
Mild	3 (27%)	2 (14%)	6 (38%)			
Moderate	3 (27%)	6 (43%)	7 (44%)			
Severe	5 (45%)	6 (43%)	3 (19%)			
Age of independent walking (months)	18 (10)	18 (1)	16 (4)	0.18		
Walking velocity (m/sec)	1.08 (0.28)	1.04 (0.44)	1.00 (0.31)			
Non-dimensional walking velocity	0.366 (0.106)	0.382 (0.159)	0.358 (0.115)	0.77		
Walking distance					0.02	0.03 (b) 0.009 (c)
<1km	5 (45%)	8 (57%)	1 (7%)			
1km-3km	3 (27%)	2 (14%)	3 (20%)			
>3km	3 (27%)	4 (29%)	11 (73%)			
FMS-5m:						
Score 4	0 (0%)	1 (7%)	0 (0%)			
Score 5	10 (91%)	11 (79%)	10 (67%)			
Score 6	1 (9%)	2 (14%)	5 (33%)			
FMS-50m:						
Score 4	3 (27%)	6 (43%)	1 (7%)			
Score 5	7 (64%)	6 (43%)	10 (67%)			
Score 6	1 (9%)	2 (14%)	4 (27%)			
FMS-500m:					0.10	0.04 (c)
Score 1	5 (45%)	8 (57%)	2 (2%)			
Score 4	3 (27%)	1 (7%)	3 (23%)			
Score 5	2 (18%)	5 (36%)	7 (47%)			
Score 6	1 (9%)	0 (0%)	3 (20%)			

Median and interquartile range (IQR) with P-value of the Kruskal-Wallis test (K-W) for numerical data. Count and percentage (%) with P-value of the Fisher's exact test (Fisher) for categorical data. Significantly different values are in bold, with P ≤ 0.05 for Kruskal-Wallis and P ≤ 0.10 for Fisher's exact test. P-values of post hoc tests were only reported when significant with (a) between KMext and KMflex-Tf, (b) between KMext and KMflex-Tn/b, and (c) between KMflex-Tf and KMflex-Tn/b. FMS: Functional Mobility Scale. FMS values were missing for one participant in the KMflex-Tn/b group

Table 2

Clinical characteristics of the three subgroups.

Table 3

Physical examination of DS subgroups.

	KMext	**KMflex-Tf**	**KMflex-Tn/b**
	(n = 11)	**(n = 14)**	**(n = 16)**
	median (IQR)	median (IQR)	median (IQR)
	or n (%)	or n (%)	or n (%)
Joint RoM and muscle length			
Hip extension, m psoas (Thomas test)			
Normal	7 (64%)	12 (86%)	12 (75%)
Limited	4 (36%)	2 (14%)	4 (25%)
Knee flexion, m rectus femoris (Duncan Ely)			
Normal	3 (27%)	10 (71%)	8 (50%)
Limited	8 (73%)	4 (29%)	8 (50%)
Knee extension, joint RoM (positive values for hyperextension)			
Median (IQR)	0 (7.5)	5 (10)	5 (6.25)
Normal	9 (82%)	14 (100%)	16 (100%)
Limited	2 (18%)	0 (0%)	0 (0%)
Knee extension, m hamstrings (Popliteal angle with contralateral knee extended)			
Median (IQR)	-45 (12.5)	-27.5 (27.5)	-37.5 (21.25)
Normal	3 (27%)	9 (64%)	8 (50%)
Limited	8 (73%)	5 (36%)	8 (50%)
Ankle dorsiflexion, m soleus (Silfverskiöld 90°)			
Median (IQR)	10 (10)	20 (8.75)	17.5 (10)
Normal	1 (9%)	3 (21%)	4 (25%)
Limited	10 (91%)	11 (79%)	12 (75%)
Ankle dorsiflexion, m gastrocnemius (Silfverskiöld 0°)			
Median (IQR)	5 (5)	10 (8.75)	10 (10)
Normal	1 (9%)	2 (14%)	4 (25%)
Limited	10 (91%)	12 (86%)	12 (75%)
Skeletal alignment			
Femoral anteversion (TPAT)			
Median (IQR)	25 (5)	30 (5)	30 (5)
Normal	8 (73%)	11 (79%)	14 (88%)
Increased anteversion	3 (27%)	3 (21%)	2 (13%)

	KMext	KMflex-Tf	KMflex-Tn/b
	(n = 11)	(n = 14)	(n = 16)
Tibial torsion (bimalleolar angle)			
Median (IQR)	25 (7.5)	30 (5)	25 (10)
Normal	3 (27%)	3 (21%)	6 (38%)
Increased external torsion	8 (73%)	11 (79%)	10 (63%)
Foot posture index (FPI-6)			
Median (IQR)	6 (5.5)	5.5 (6.75)	6.5 (6)
Normal	5 (45%)	9 (64%)	10 (63%)
Increased pronation (planovalgus)	6 (55%)	4 (29%)	5 (31%)
Increased supination (cavovarus)	0 (0%)	1 (7%)	1 (6%)

All measures were compared to age-related norm values with mean ± 1SD as cut-off to define deviations (Mudge et al. 2014; Redmond et al. 2008). Values in this table did not significantly differ between subgroups. IQR, interquartile range; TPAT, trochanteric prominence angle test; RoM range of motion.

5. Discussion

This study aimed to characterise kinetic strategies in gait of patients with DS by evaluating the M_S and defining subgroups based on internal knee extension moments and trunk lean. Increased M_S were observed and three main strategies were identified with characteristic kinematic and kinetic deviations.

The M_S equals force in the direction of the hip-ankle axis times knee eccentricity and is thus mainly determined by GRF magnitude and knee flexion angles (Hof 2000). Walking velocity is known to affect both factors and was significantly different between the DS and TD. The absence of an association in midstance, however, suggested that M_S abnormalities were not just walking velocity effects. Knee flexion angles on the other hand were significantly increased in the three subgroups and correlated with M_S. The increased M_S suggested that participants with DS require more muscular effort for stance limb support. Future studies on EMG activity should test this hypothesis. Three subgroups were distinguished based on strategies that could influence the knee eccentricity.

Although six patients in *KMext* walked with forward trunk lean, they all failed to align the GRF in front of the knee. The resulting kinematic pattern of flexion in hip, knee and ankle with a neutral pelvis position and persistent internal knee extension moment can be defined as 'uncompensated crouch gait' (Rodda et al. 2004; Jon R. Davids and Bagley 2014). Persistent

knee extension moments are expected to require extra muscle activity and thereby lead to higher energy costs that could impact functional mobility in this subgroup.

Even though *KMflex-Tf* also showed increased flexion in the three lower limb joints, the forward trunk lean strategy might reduce M_S. However, anterior pelvic tilt and hip flexion increased as a consequence and evoked increased internal hip extension moments, so the resulting M_S remained high compared to TD. The required increased hip extensor activity makes this pattern energetically inefficient. The trunk and pelvis position together with internal knee flexion moments can be classified as 'compensated crouch gait' (Jon R. Davids and Bagley 2014). It remains unclear whether trunk lean was purely a support strategy or reflected underlying trunk control deficits (Heyrman et al. 2014).

In contrast to the other subgroups, internal knee flexion moments were attained without forward trunk lean in *KMflex-Tn/b*. The observation of normal internal plantar flexion moments in early- and midstance suggested functional plantar flexion – knee extension couple. However, M_S were still increased compared to TD, combined with increased flexion angles in hip, knee and ankle. Nevertheless, all deviations remained close to normative values, indicating that gait in this subgroup was only mildly affected.

Our subgrouping process was based on kinetic strategies, and therefore did not follow the kinematic classification proposed by Di Marco et al. (2019) (Di Marco et al. 2019). In that previous study, an 'atypical crouch' gait pattern was distinguished from a 'straight' pattern based on knee angle at initial contact. Their findings of anterior pelvic tilt, increased hip and knee flexion and external foot progression angles were confirmed in the present study. Furthermore, three main kinetic strategies were revealed that underly the observed deviations. These results imply that clinical evaluation of gait should pay attention to knee angles, trunk lean and M_S. When forward trunk leaning is observed, kinetic analysis can reveal whether this potential compensation for crouch gait was successful.

Lever arm dysfunction and weakness or impaired control of muscles were identified as possible causes of crouch gait in patients with cerebral palsy (Gage 1993). External tibial torsion and pes planovalgus were frequently observed in patients with DS, decreasing the lever arm of the foot, which may disrupt the plantar flexion-knee extension couple. However, these malalignments we equally distributed over the three subgroups and might not impose the kinetic strategies. Measuring muscle strength was too challenging owing to cognitive impairments.

Age differences revealed that compensated crouch gait was mostly observed in younger

children, which might evolve to uncompensated crouch in adolescence. These findings are in line with previous research suggesting progressive deterioration of gait (Rodda et al. 2012) The progression of crouch gait as observed in cerebral palsy, involves the risk to develop hamstrings tightening with knee flexion contractures and loss of functional independency (O'Sullivan et al. 2018). Functional mobility was indeed more limited in *KMext*. Hamstrings tightening was present in half of the participants, independent from their kinetic strategies, but flexion contractures at the knee joint were only observed in *KMext* (two patients). Longitudinal studies are needed to document the evolution and detect prognostic factors.

Other clinical characteristics did not differ significantly between subgroups. This may suggest that epileptic activity and cognitive development were not determinative for gait strategies. However, due to small numbers of participants per subgroup and heterogeneity within DS, associations might be hard to detect. Ideally, gait interventions prevent crouch gait development and help patients achieve an overall more efficient gait pattern with a favourable functional outcome. Further research on causal mechanisms behind mechanical deviations in DS could guide therapy.

The M_S is limited to the sagittal plane, where major kinetic strategies were situated. However, coronal and transverse plane deviations were also observed. Internal hip abduction moments contribute to stance limb support and were characterised by a decreased second peak, which might be explained by step width or lateral trunk motion. Cross-plane interactions could be the subject of future research.

5.1 Limitations

A first limitation of this study were cognitive and behavioural problems that challenged participants to comply with rigorous protocols of gait analysis. This has led to the exclusion of four participants. The sample was large and therefore strongly representative for a rare disorder. Nevertheless, it remains uncertain whether the included patients' gait was representative for patients with the most severe cognitive and behavioural problems. A second limitation was the large age range of the included patients. Assembling childhood, adolescent and young adult clinical presentation may have increased the heterogeneity of the sample, but also offered an opportunity to demonstrate the diversity in gait deviations from early to adult age. This study accounted for effects of height and weight differences by non-dimensional normalisation of spatiotemporal parameters and joint moments (Hof 1996). Furthermore, the use of video images to assess trunk lean was less objective and reliable than quantitative registration using trunk markers, which would be recommended for future instrumented gait analysis in this population (Romkes et al. 2007).

6. Conclusion

An overall inefficient walking pattern was evident in patients with DS. Increased MS suggested that more extensor muscle effort was required to maintain stance limb stability. Forward trunk lean was mostly employed by younger patients with various degrees of success to attain alignment of the ground reaction force that facilitates knee extension. Closer-to-normal kinetic strategies were as well observed, with mild gait deviations and a favourable functional outcome.

7. Acknowledgements and conflict of interest statement

The authors thank the participants and their families for their cooperation and prof. dr. Guy Molenaers for his advice. This study was supported by the Flemish Research Council (grant number T003116N), the University of Antwerp, the University Hospital of Antwerp and the KU Leuven. The authors declare that they have no conflict of interest.

Appendix

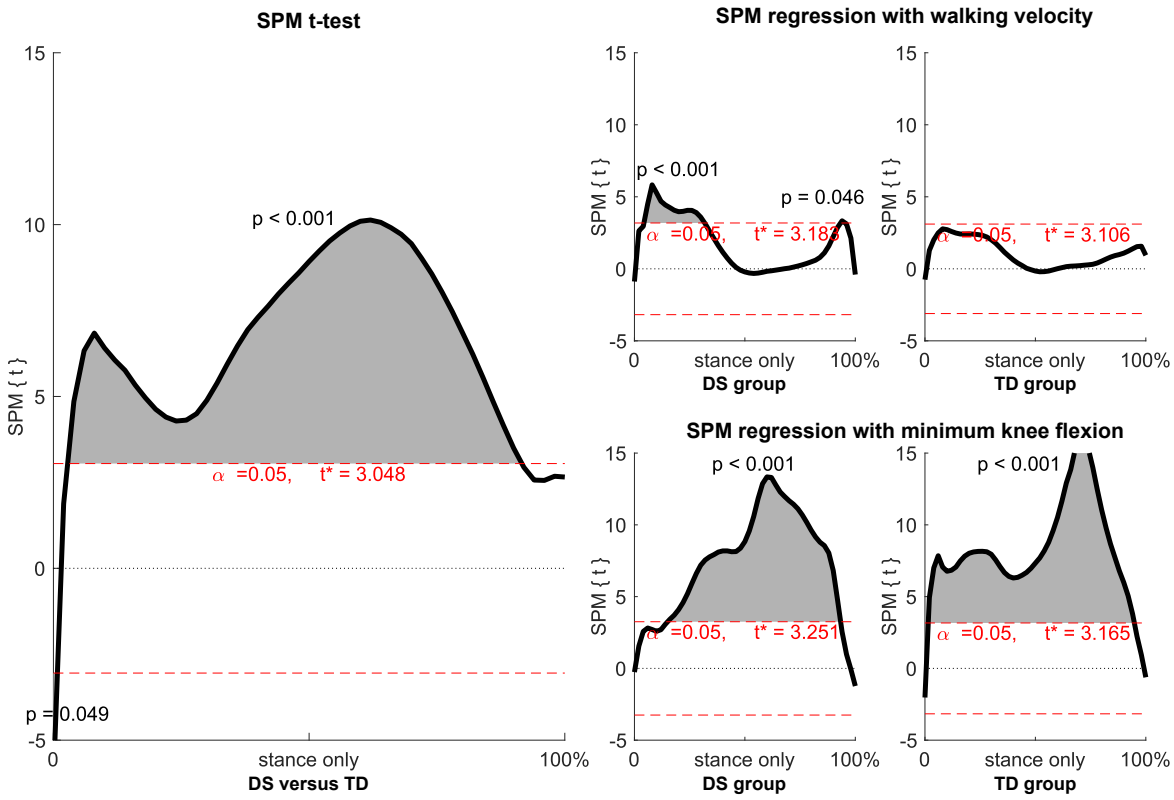

Figure A1. SPM inference curves accompanying figure 2: The support moment and its relation to walking velocity and knee flexion. Left: The SPM{t} curve of the t test statistics represents the difference between the support moment in the typically developing (TD) group and the Dravet Syndrome (DS) group over the stance phase. Right: The SPM{t} curve expresses the effect magnitude of non-dimensional walking velocity (upper) and minimum knee flexion angle in midstance (lower) on the support moment in both groups. Red dashed lines indicate the critical treshold (t*) for α = 0.05. Shaded areas with P values are clusters with significant differences (t-test) or association (regression).

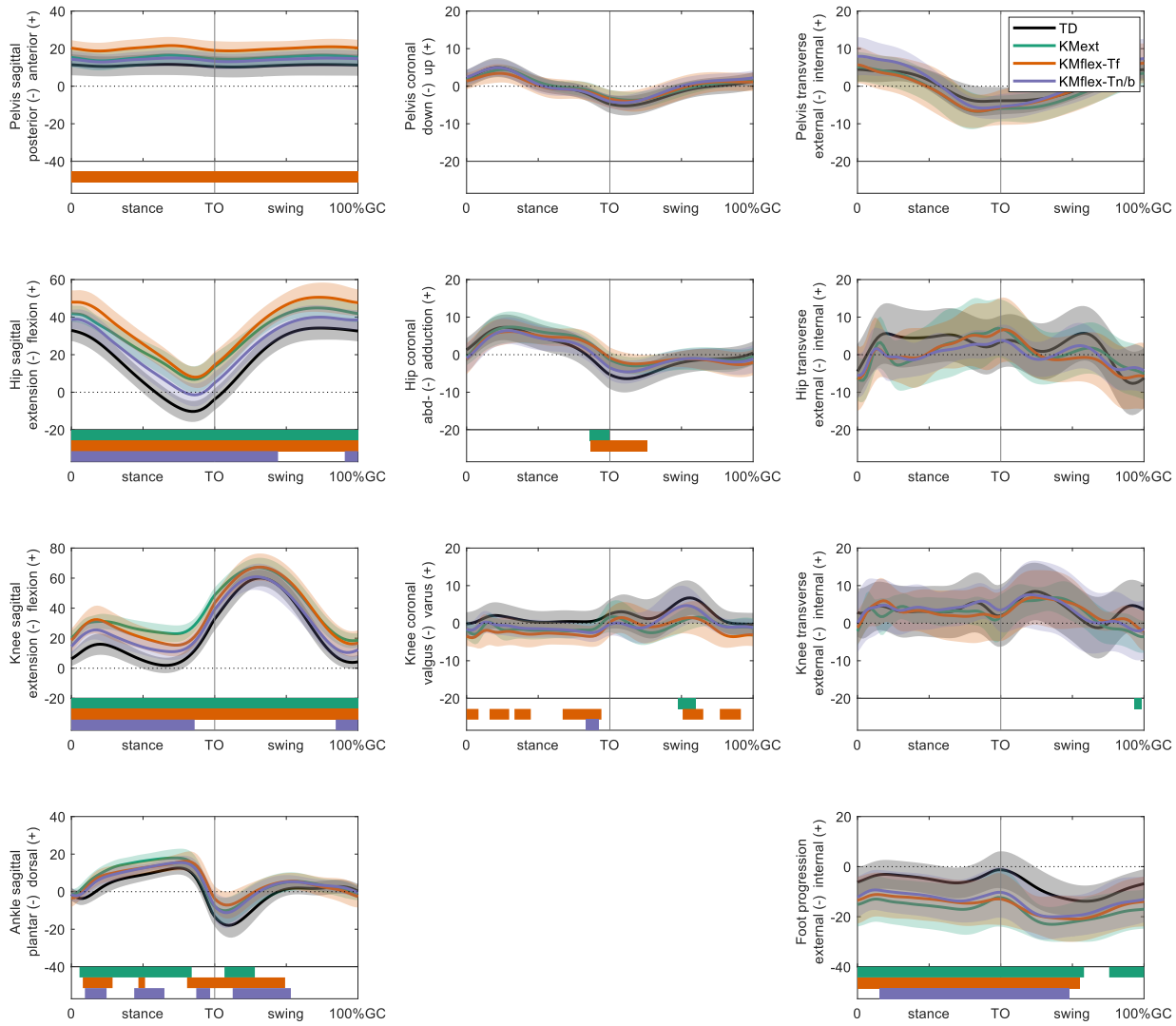

Figure A2. Comparison of kinematics in the three planes between Dravet Syndrome subgroups and typically developing (TD) controls. Group averaged curves and 1SD regions are plotted. Horizontal bars represent clusters with significant differences (SPM t-tests) comparing subgroups with the TD group. TO, toe off; GC, gait cycle

Figure A3. SPM inference curves accompanying figure 3: Comparison of kinematic and kinetic curves between Dravet Syndrome (DS) subgroups and typically developing (TD) controls. The SPM{t} curves of the t test statistics represent the difference between the DS subgroup (KMext, KMflex-Tf or KMflex-Tn/b) and the TD group. Red dashed lines indicate the critical treshold (t*) for Bonferroni corrected α = 0.05/3. Shaded areas with P values are clusters with significant differences. The gait cycle on the x-axis was normalized for stance (50%) and swing (50%) phase, except for the support moment, where only stance phase (100%) was analyzed. TO, toe-off

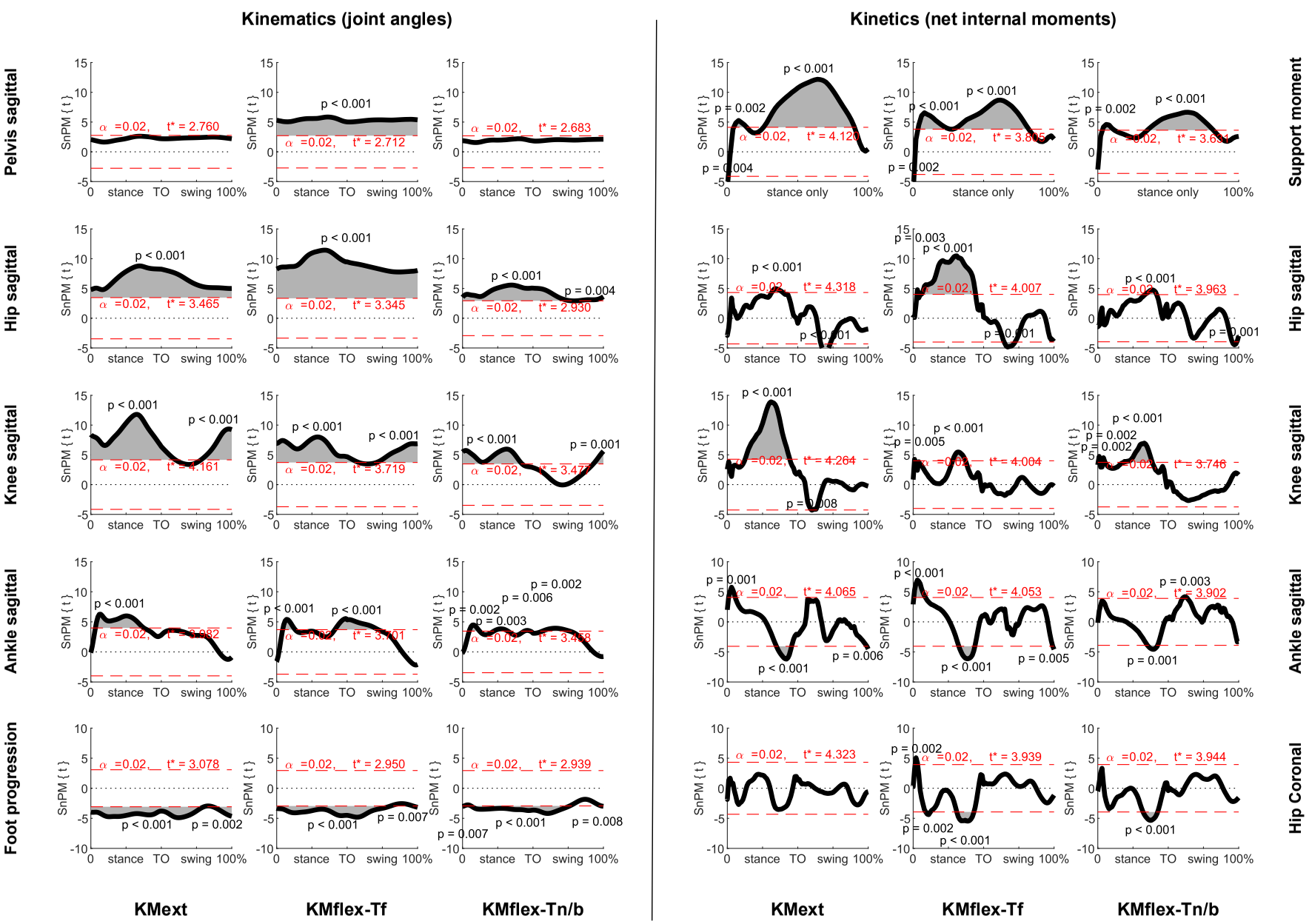
Kinematics (joint angles)
Kinetics (net internal moments)
Pelvis sagittal
Hip sagittal
Knee sagittal
Ankle sagittal
Foot progression
Support moment
Hip sagittal
Knee sagittal
Ankle sagittal
Hip Coronal
KMext
KMflex-Tf
KMflex-Tn/b
SnPM{t}
stance
TO
swing
stance only
100%

Table A1

Characteristics of individuals in the DS group.

	Age (years) and gender	BMI	SCN1A mutation type	Nucleotide change	De novo	Age of onset epilepsy (months)	Current epileptic activity	Level of ID	Age of independent walking (months)	Walking distance	FMS
KMflex subgroup	6.4 m	14.3	missense	c.3714A>C	no	11	mild	mild	20	1km-3km	5/5/1
	7.4 m	14.7	frameshift	c. 5536_5539del	yes	4	mild	mild	18	1km-3km	6/6/6
	13.4 f	17.9	nonsense	c.4219C>T	unknown	8	severe	moderate	13	1km-3km	5/5/5
	16.1 f	27.0	missense	c.4294A>G	yes	3	mild	moderate	30	<1km	5/5/1
	17.1 f	29.3	missense	c.4168G>A	yes	4	free	mild	14	>3km	5/5/5
	17.1 m	14.3	missense	c.4223G>T	yes	8	mild	moderate	13	>3km	5/5/4
	19.2 f	23.7	deletion	c.1200_1202delTGA	yes	3	mild	severe	46	<1km	4/5/1
	19.8 m	24.0	missense	c.680T>G	unknown	3	severe	severe	27	<1km	5/5/1
	20.7 m	14.4	frameshift	c.4497delT	yes	6	severe	severe	18	<1km	4/5/1
	24.8 m	19.2	splice site	c.4338+1G>A	yes	5	severe	severe	13	>3km	5/5/4
	25.7 f	28.2	missense	c.1178G>A	yes	6	severe	severe	18	<1km	4/5/4
KMext-Tf subgroup	5.2 m	15.1	missense	c.5735G>C	yes	5	mild	moderate	18	1km-3km	4/4/1
	5.2 f	17.2	missense	c.2836C>T	unknown	4	mild	moderate	37	<1km	5/5/1
	5.6 m	16.3	missense	c.4346T>C	yes	6	mild	moderate	18	<1km	4/5/1
	6.7 m	13.7	nonsense	c.1348C>T	yes	8.5	severe	moderate	18	>3km	5/5/5
	7.2 f	19.7	intragenic deletion	(exon 1-7)	unknown	5	severe	severe	14	<1km	6/6/4
	7.5 m	13.2	missense	c.406T>C	yes	6	free	mild	18	>3km	5/5/5
	8.4 f	19.8	missense	c.1178G>A	yes	4	free	severe	18	<1km	5/5/1
	10.1 f	15.6	missense	c.296T>A	yes	4	mild	severe	36	<1km	4/5/1
	10.6 f	18.0	nonsense	c.1738C>T	yes	5	mild	severe	18	<1km	4/5/1
	10.8 m	13.4	nonsense	c.969T>G	yes	3	free	mild	19	>3km	5/5/5
	14.7 f	23.2	missense	c.4633A>G	yes	11	moderate	severe	unknown	1km-3km	6/6/5
	15.8 m	17.0	missense	c.5150T>C	yes	4	moderate	moderate	20	<1km	4/5/1
	17.0 m	25.7	frameshift	c.550dupT	unknown	8	mild	moderate	unknown	>3km	5/5/5
	22.1 f	26.4	missense	c.2902T>G	yes	11	moderate	severe	15	<1km	4/5/1

	Age (years) and gender	BMI	SCN1A mutation type	Nucleotide change	De novo	Age of onset epilepsy (months)	Current epileptic activity	Level of ID	Age of independent walking (months)	Walking distance	FMS
KMext-Tn/B subgroup	5.2 m	14.8	missense	c.2791C>T	yes	3	moderate	mild	16	>3km	6/6/6
	5.9 m	14.5	missense	c.301C>T	yes	3.5	free	moderate	16	<1km	4/5/1
	6.8 f	15.6	frameshift	c.4554dupA	yes	6	moderate	moderate	14	>3km	5/5/5
	8.4 m	13.5	nonsense	c.664C>T	yes	7	free	mild	15	>3km	6/6/6
	9.3 f	12.7	missense	c.1178G>A	unknown	4	free	moderate	14	>3km	5/5/5
	9.3 m	12.7	nonsense	c. 2134C>T	yes	5	mild	mild	20	>3km	5/5/5
	10.7 m	16.5	frameshift	c.657_658delAG	yes	6	severe	severe	22	1km-3km	5/5/1
	10.8 f	13.1	frameshift	c.3503dupT	yes	5	moderate	mild	18	>3km	5/5/4
	11.4 m	22.0	missense	c.2791C>T	yes	9	mild	mild	unknown	unknown	unknown
	11.9 f	19.3	frameshift	c.429_430delGT	yes	3	free	mild	15	1km-3km	5/5/4
	17.5 m	17.0	micro-duplication	c.3430-?_4002+?dup	unknown	4	severe	moderate	13	>3km	6/6/5
	17.6 f	27.3	frameshift; splice site	c.[1169InsC]; [1170+1G>A]	yes	4.5	mild	moderate	18	>3km	5/5/5
	19.2 f	26.3	nonsense	c.58C>T	yes	5	mild	moderate	14	>3km	5/5/5
	22.2 f	25.9	missense	c.5534A>C	no	10	moderate	moderate	16	>3km	5/5/4
	24.0 m	18.1	splice site	c.4853-1G>C	yes	7	free	severe	18	>3km	6/6/6
	26.1m	15.8	missense	c.680T>C	yes	4.5	free	severe	unknown	1km-3km	5/6/5

BMI = Body Mass Index, ID = Intellectual Disability, FMS = Functional Mobility Scale (5m/50m/500m), m = male, f = female

Table A2

Spatiotemporal parameters did not significantly differ between subgroups.

	KMext	KMflex-Tf	KMflex-Tn/b
	(n = 11)	(n = 14)	(n = 16)
	median (IQR)	median (IQR)	median (IQR)
Spatiotemporal parameters			
Walking velocity (m/sec)	1.08 (0.28)	1.04 (0.44)	1.00 (0.31)
Non-dimensional walking velocity	0.366 (0.106)	0.382 (0.159)	0.358 (0.115)
Cadence (steps/sec)	1.92 (0.27)	2.08 (0.53)	2.02 (0.56)
Non-dimensional cadence	0.600 (0.083)	0.599 (0.091)	0.562 (0.084)
Step length (m)	0.51 (0.17)	0.46 (0.11)	0.52 (0.14)
Non-dimensional step length	0.595 (0.156)	0.637 (0.213)	0.659 (0.101)
Step width (m)	0.21 (0.09)	0.17 (0.06)	0.16 (0.03)
Non-dimensional step width	0.221 (0.100)	0.249 (0.107)	0.203 (0.056)
Stance time (%GC)	61.7 (3.2)	60.9 (5.7)	59.6 (3.6)

IQR, interquartile range; GC, gait cycle

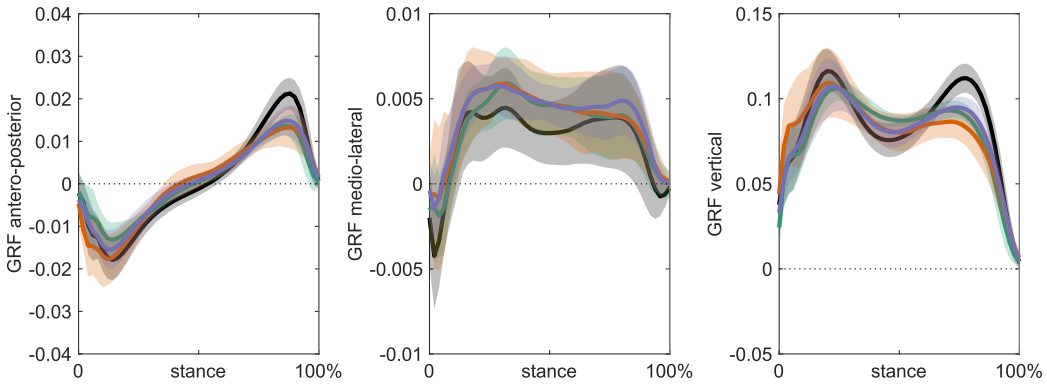

Figure A4. The three components of the ground reaction force (GRF) vector for the three subgroups (colours) and the TD group (black). Normalized for body weight.

Chapter 4

Foot-floor contact pattern in children and adults with Dravet Syndrome

Chapter 4

Foot-floor contact pattern in children and adults with Dravet Syndrome

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1. Abstract

Background: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy characterized by severe drug-resistant seizures and associated with cognitive and motor impairments. Walking problems are frequently observed. As the foot plays a key role during walking, compromised foot function can be a feature of deviant gait.

Objective: To investigate foot function in DS by characterizing foot-floor contact patterns using pedobarography.

Methods: A total of 31 children and adults were included in the DS group (aged 5.2-32.8 years, 17 female, 174 steps) and 30 in the control group (aged 6.0-32.9, 16 female, 180 steps). The foot-floor contact pattern was evaluated based on progression, length and smoothness (spectral arc length) of the centre of pressure (CoP). Linear mixed models were used to identify differences between non-heel strikes and heel strikes and between the DS and control group.

Results: Fifteen participants with DS showed inconsistency in the type of foot-floor contact (heel strikes and non-heel strikes). Heel strikes of participants with DS had significantly reduced time of CoP under the hindfoot and increased time under the midfoot region compared to the control group. Significant time and age effects were detected.

Conclusions and Implications: Deviant foot-floor contact patterns were observed in DS. Possible gait immaturity and instability as well as implications for interventions are discussed.

2. Introduction

Dravet Syndrome (DS) is a developmental and epileptic encephalopathy with an estimated prevalence between 1/15000 and 1/40000. In at least 80% of cases, it is caused by mutations in the gene encoding the sodium channel type I alpha subunit, *SCN1A* (Claes et al. 2001; Brunklaus et al. 2012). The syndrome is characterized by drug resistant infantile onset seizures accompanied by cognitive, behavioural and motor impairments (Dravet 2011; Scheffer et al. 2017). Children with DS show a delay in motor development before the age of two, often with a delayed achievement of independent walking (Verheyen, Verbecque, et al. 2019; Rodda et al. 2012; Gitiaux et al. 2016). Diverse gait alterations have been described in DS, with about half of the investigated cases presenting a gait pattern which resembles crouch gait (Wyers, Van de Walle, Hoornweg, et al. 2019; Rodda et al. 2012; Di Marco et

al. 2019). Although gait problems are a major concern for children and adults with DS and their caregivers (Camfield, Camfield, and Nolan 2016; Villas, Meskis, and Goodliffe 2017), scarce literature has addressed this topic and especially quantitative assessments of gait deviations are lacking (Wyers, Van de Walle, Hoornweg, et al. 2019).

The foot plays a key role during walking as it supports the weight of the body on the ground. The dynamically functioning foot is required to be sufficiently flexible to provide stability on any surface and at the same time to be a rigid lever able to transmit propulsive forces for an efficient walking pattern (Bevans 1992). Detailed evaluation of foot function is possible using three dimensional motion analysis with multi-segment foot models (Deschamps et al. 2011; Leardini et al. 2019; Di Marco et al. 2016). However, this procedure requires high levels of participant collaboration, which makes it a less feasible option in DS due to cognitive and behavioural problems. Less complex approaches such as pedobarography may provide meaningful insight into foot function. In pedobarography, pressure platforms are used to analyse the pressure distribution under the foot. Quantitative measures enable the objective detection of disturbed foot-floor contact patterns (Deschamps et al. 2015).

A relevant plantar pressure measure is the centre of pressure (CoP) and its trajectory on the plantar surface, also referred to as 'gait line'. The CoP is defined as the centroid of all external forces acting on the plantar surface of the foot and is often used as an indirect measure of neuromuscular control (Fuller 1999; Jameson et al. 2008). A mature foot-floor contact pattern is characterized by a heel strike at initial contact followed by a fluent movement of the CoP from the medial aspect of the heel over the lateral side of the foot, ending with a quick medial shift on the forefoot. Impaired motor control may affect the ability to consistently perform heel strikes. Deviations in CoP trajectories may reflect compromised foot function and pathological gait (Jameson et al. 2008). This study aims to investigate foot function in children and adults with DS by characterizing foot-floor contact patterns using pedobarography. We hypothesize that differences in progression, length and smoothness of the CoP trajectory can be detected between patients with DS who consistently perform heel strikes, those who are not able to consistently perform heel strikes and able-bodied controls.

3. Methods

3.1 Setting

Data collection was performed at the Laboratory of Clinical Analysis and Biomechanics of Movement and Posture, University Hospital of Padua, Italy. Patients with DS were recruited at Neurological Institute Carlo Besta, Milan, Italy, University Hospital of Padua, Italy and Verona University Hospital, Verona, Italy. Measurements took place between May 2015 and October 2019. The study was approved by the Ethical Committee of the Padua University Hospital (protocol number 4276/AO/17).

3.2 Inclusion

All participants with a minimum age of five years and a genetically confirmed diagnosis of DS were eligible. Exclusion criteria were the inability to walk without assistance, or the occurrence of a convulsive seizure within 24 hours prior to the examination. Age-matched able-bodied volunteers were enrolled as control group. Exclusion criteria for the control group were a history of neurological or orthopaedic disorders. All participants and their legal guardians provided written informed consent.

3.3 Data collection

Height, weight and foot length (from the most proximal apex of calcaneus to the most distal apex of the toes) were measured and inspection of the foot posture in stance was performed. Pedobarographic data were collected using the midgait method (McPoil et al. 1999) on a walkway with an embedded plantar pressure platform (100 Hz, 4 sensors/cm², from 10 to 12720 kPa, 47.5x32.0 cm2, max force: 193 kN, emed-q®, Novel GmbH, Munich, Germany). Participants walked barefoot at self-selected walking velocity and were instructed not to look down or target the pressure mat. As long as participant cooperation was ensured, trials were repeated until at least six successful steps per side were collected. In case participants were less cooperative, only the side(s) with a minimum of three successful steps were included. Due to behavioural issues, all 'clean' steps on the platform were collected, even steps that were less representative for the participant's usual gait pattern. Afterwards, steps considered most representative were identified in a standardized manner. Hereto, custom made MATLAB® scripts (R2018a, The Mathworks Inc, Natick, MA, US) were used to calculate correlations between all pressure distribution images within each participant (appendix A). For each side, the three footprints with the highest correlation among each other were selected for further analysis.

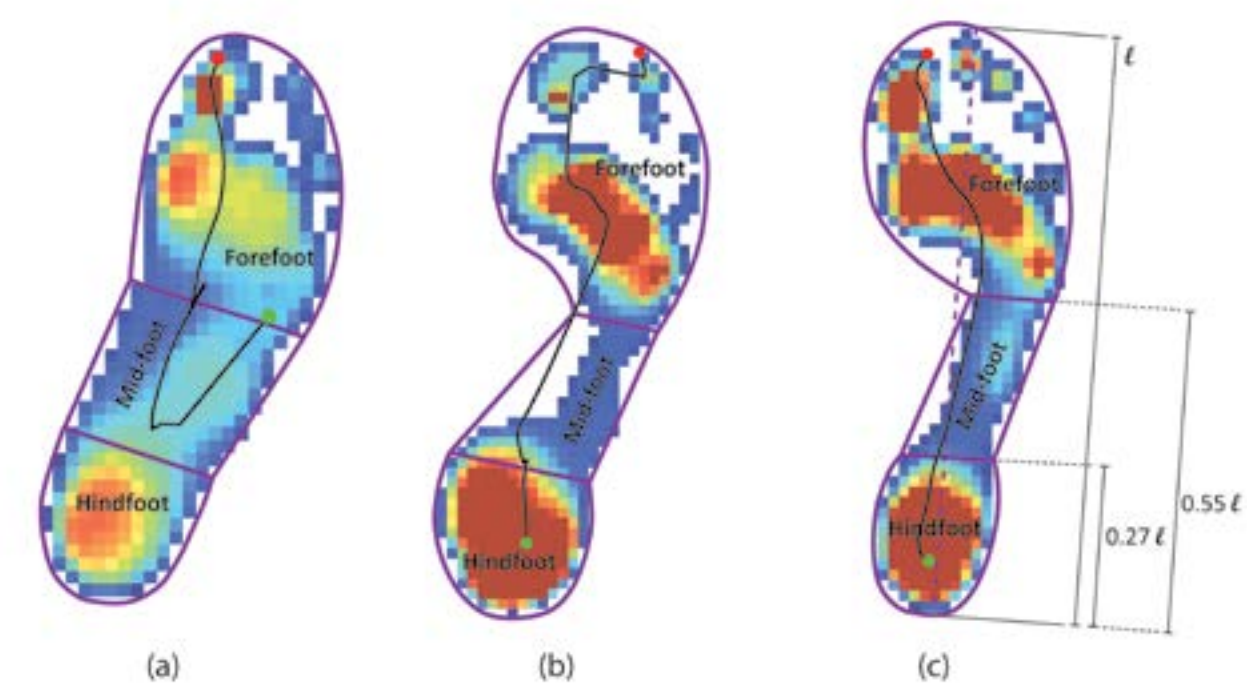

Figure 1 Example images of centre of pressure trajectories on maximal pressure images of a) non-heel strike by a participant with DS, b) heel strike by a participant with DS and c) heel strike by a typically developing volunteer. Purple lines indicates the applied masking to identify the hind-, mid- and forefoot regions, with those being separated by two lines perpendicular to the longitudinal axis of the footprint (purple dashed line in (c): one at 27% of the heel-toe distance (l) to separate hindfoot and midfoot; and one at 55% to separate midfoot and forefoot.

3.4 Processing

The longitudinal axis of the foot was determined as the bisect between the tangents for the medial and lateral sides of the maximum pressure picture. Three regions were identified based on two lines perpendicular to the longitudinal axis as defined in the platform's standard software: one at 27% of the heel-toe distance to separate hindfoot and midfoot, and one at 55% to separate midfoot and forefoot (figure 1c). The toes were included in the forefoot region (Multimask v23 Novel GmbH, Munich, Germany). Manual quality control assured correct masking and confirmed that all included steps were full footprints. The CoP was determined as the weighted centroid of the total number of active sensors for each data sample. Based on the region where the first CoP point was situated, steps were identified as heel strikes (hindfoot) or non-heel strikes (mid- or forefoot region). A low pass fourth order Butterworth filter at 20 Hz was applied to the CoP trajectory over time, using a reflection technique to avoid edge effects at the beginning and end of the signal (De Cock et

al. 2008). After filtering, six parameters were calculated as presented in table 1. Filtering and parameter calculations were implemented in MATLAB®.

The CoP progression (CoPP) was calculated for the three foot regions as the time during which CoP was situated under that region relative to total contact time (TCT). Length ratio was defined as the CoP trajectory path length normalized by clinically measured foot length. Mature foot-floor contact patterns were expected to have a length ratio of approximately one, with larger values indicating less efficient gait due to additional or compensatory movements. Smoothness of the CoP trajectory was assessed by calculating the spectral arc length (SPARC), the arc length of the Fourier magnitude spectrum within an adaptive frequency range. This smoothness index proved to be sensitive, robust to measurement noise and independent of temporal movement scaling (Balasubramanian et al. 2015). SPARC was calculated for the medio-lateral (M-L SPARC) and antero-posterior (A-P SPARC) components of the CoP displacement vector, using code provided by Balasubramanian et al. (2015) (Balasubramanian et al. 2015). SPARC is a negative number with larger absolute values indicating more interruptions and thus less smooth CoP trajectories.

Table 1
Definition of the main outcome variables.

CoP trajectory	Parameter	Definition
Progression	CoPP hindfoot	CoP progression on hindfoot (% of total contact time)
	CoPP midfoot	CoP progression on midfoot (% of total contact time)
	CoPP forefoot	CoP progression on forefoot (% of total contact time)
Length	Length Ratio	CoP trajectory path length (cm) / foot length (cm)
Smoothness	M-L SPARC	Medio – lateral spectral arc length
	A-P SPARC	Antero – posterior spectral arc length

CoPP, center of pressure progression; CoP, centre of pressure; SPARC, Spectral arc length; M-L, medio-lateral; A-P, antero-posterior.

3.5 Statistical analysis

Descriptive statistics were computed for demographics and step characteristics. The demographic data were compared between groups using Mann-Whitney U tests, after Shapiro-Wilk tests did not confirm a normal distribution.

Non-heel strikes were only observed in the DS group and resulted in v-shaped CoP trajectories (figure 1a). Because of this different shape, it would not have been appropriate to compare them with heel strikes from the control group. We therefore used a two-stage approach. In the first stage, the effect of the type of initial contact on CoP parameters was analysed within the DS group and non-heel strikes were omitted in stage two. In the second stage, distinction was made between participants with DS that always performed heel strikes and those who inconsistently switched between non-heel strikes and heel strikes. Comparison of CoP parameters was then performed between the two DS subgroups ('DS_consistent' and 'DS_inconsistent') and the control group.

Linear mixed models were fitted to assess the effect of the type of initial contact (non-heel strike or heel strike) and group (DS_consistent, DS_inconsistent or control) respectively, on the main outcome parameters. Age, TCT and side (left, right) were added as fixed effects. To account for non-independence of observations, subject and side, nested within subject, were entered as random effects. Significance of the fixed effects was tested using a likelihood ratio test. We first fitted linear mixed models testing the effect of type of initial contact on each of the six outcome measures within the DS group. Subsequently, we fitted linear mixed models to detect differences between the DS subgroups and control group for all outcome parameters. If the existence of a significant difference was revealed, post hoc pairwise comparisons (Bonferroni) using estimated marginal means, were performed to detect differences between groups. All statistical analyses were performed in R (v 4.0.0, R Foundation, Vienna, Austria, packages 'lme4' and 'emmeans') (Bates et al. 2015). Details on the linear mixed models analysis can be found in appendix B.

The nominal significance level was set at $P<.05$, but may not be appropriate as a cut-off for the linear mixed models, because multiple hypotheses were tested. Since there were moderate correlations between the six outcomes, a Bonferroni correction would be too conservative. A Benjamini-Hochberg correction, controlling for a false discovery rate of 0.05, was applied to interpret the results of the linear mixed models (Benjamini and Hochberg 1995).

4. Results

4.1 Demographics and step characteristics

In total, 31 children and adults with DS (174 steps) and 30 age-matched typically developing volunteers (180 steps) with an age range from 5.2 to 32.9 years were included in the study (table 2). Out of 46 eligible candidates with DS, 15 patients needed to hold hands for guidance or support, could not repeat trials until a sufficient number of steps were collected or did not walk in a straight line in a representative manner and were thus excluded. Among the 31 participants with DS, 17 had planovalgus feet (pronation) and four hindfoot varus (supination), of whom 12 wore insoles with arch and hindfoot support or orthopaedic shoes (table 2).

Table 2

Demographics per group and subgroup.

Demographics	**DS**			**Control (n = 30)**
	Total (n=31)	**DS_consistent subgroup (n=15)**	**DS_inconsistent subgroup (n=16)**	
Age (year)	13.0 (5.2; 32.8)	15.1 (6.9;32.8)*	11.1 (5.2;24.6)*	13.5 (6.0; 32.9)
Gender (male/ female)	14 / 17	7 / 8	7 / 9	14 / 16
Height (cm)	147.0 (106.0; 194.5)	155.5 (119.5; 194.5)*	139.8 (106.0;164.0)*	160.5 (117.0; 180.5)
Weight (kg)	42.0 (18.5; 83.5)	51.0 (20.0; 83.5)	35.0 (18.5; 69.5)	48.5 (19.5; 81.5)
Foot morphology (n):				
Pronation (planovalgus)	17	6	11	
Supination (varus)	4	3	1	
Neutral	10	6	4	
Insoles or orthopaedic shoes (n)	12	5	7	

Median (min; max); * significant difference between DS subgroups. DS, Dravet Syndrome; n, number of participants.

Out of a total of 174 steps in the DS group, 139 (80%) were heel strikes and 34 (20%) were non-heel strikes (eight with first CoP on the midfoot region and 27 on the forefoot region). The non-heel strikes were observed in 16 participants with DS of which one always performed forefoot strikes while the others varied with heel strikes. These 16 participants formed the DS_inconsistent subgroup with a median age of 11.1 years (range 5.2 – 24.6 years). The 15 participants with DS who always performed heel strikes, formed the DS_consistent subgroup with a median age of 15.1 years (range 6.9 – 32.8 years). The DS_inconsistent subgroup was significantly younger (*P*=.03) with lower height (*P*=.03) than the DS_consistent subgroup.

4.2 Stage 1: Comparison of non-heel strikes with heel strikes within participants with DS

Linear mixed models compared heel strikes with non-heel strikes within the DS group, accounting for age and total contact time (TCT). The likelihood ratio test (χ^2) revealed a significant difference between the two types of initial contact for all parameters except CoPP midfoot and M-L SPARC. When controlling for age and TCT, the CoPP hindfoot was significantly shorter (*P*<.001), while CoPP forefoot was longer (*P*<.001) in case of a non-heel strike, with increased Length Ratio (*P*<.001) and decreased smoothness on A-P SPARC (*P*<.001; figure 2). Detailed statistical output is reported in appendix B.

One outlier with a length ratio of 2.50 was observed among the non-heel strikes in the DS group. This outlier did not alter the conclusions on the effect of type of initial contact.

4.3 Stage 2: Comparison of heel strikes between DS subgroups and typically developing volunteers

When comparing heel strikes between the DS subgroups and control group, accounting for TCT and age, the likelihood ratio test (χ^2) detected a significant difference for CoPP hindfoot (*P*=.002) and CoPP midfoot (*P*<.001). Post hoc pairwise comparison revealed decreased CoPP hindfoot (*P*=.003) and increased CoPP midfoot (*P*<.001) in the DS_inconsistent subgroup compared controls. Other parameters did not differ significantly (figure 2). Detailed statistical output is reported in appendix B.

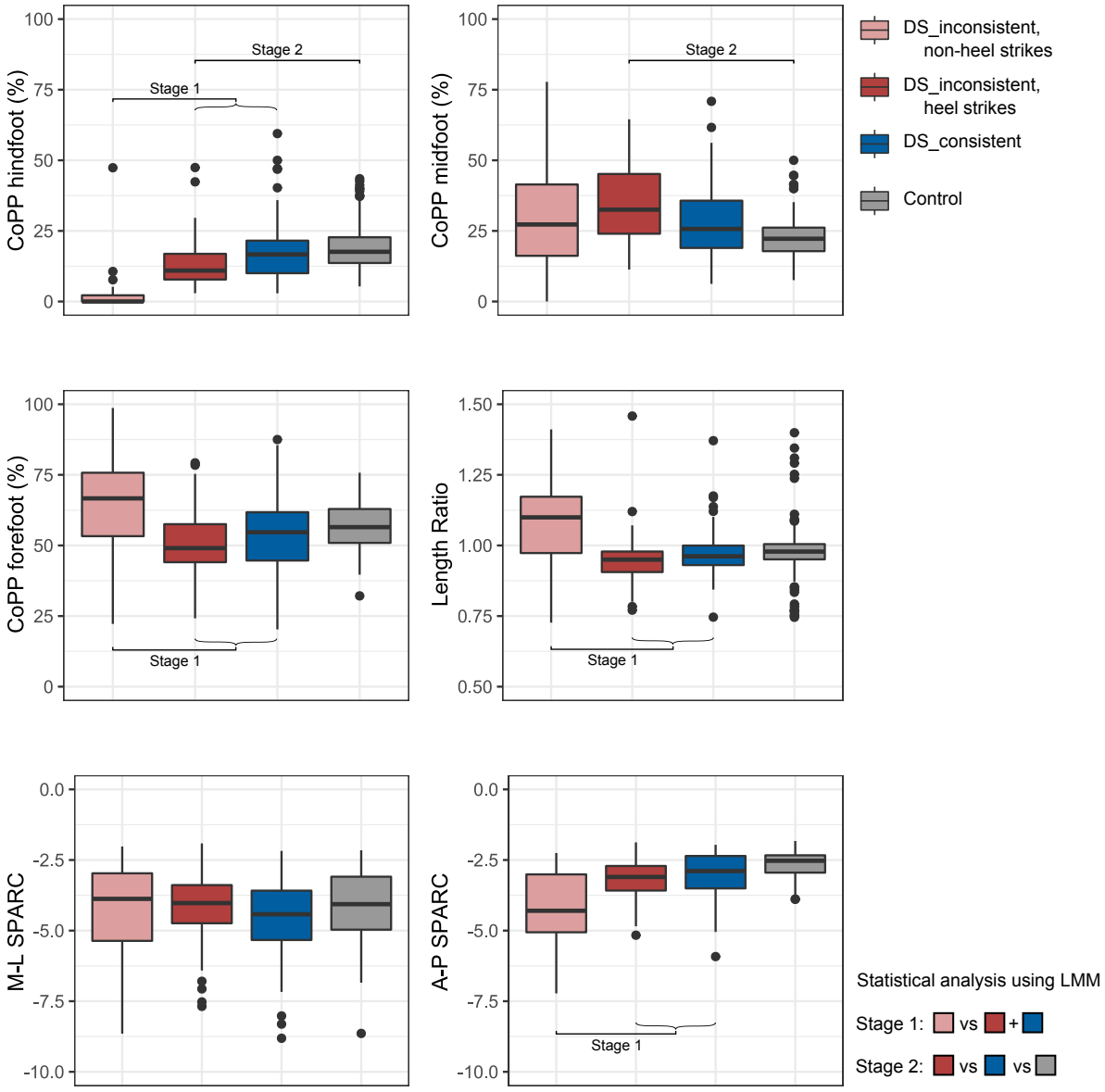

Figure 2. CoP trajectory parameters per (sub)group with subdivision of heel strikes and non-heel strikes. Significant differences where detected using linear mixed models (LMM) controlling for age and total contact time in two stages: between non-heel strikes and heel strikes within DS (Stage 1) and between heel strikes of DS_inconsistent, DS_consistent and control group (Stage 2). DS, Dravet Syndrome; CoPP, centre of pressure progression; SPARC, Spectral arc length; M-L, medio-lateral; A-P, antero-posterior.

4.4 Relation with TCT and age

In addition to group effects, the linear mixed models investigated the effects of TCT and age on the different CoP trajectory parameters. In stage1, TCT had a significant effect on all CoP trajectory parameters, while age did not show any significant effect. With increasing TCT, an increase of CoPP hindfoot (P=.03), CoPP midfoot (P=.002) and Length Ratio (P=.03) was observed and a decrease of CoPP forefoot (P<.001), M-L SPARC (P<.001) and A-P SPARC

(*P*<.001). In stage 2, significant effects of age and TCT were observed. With increasing TCT, CoPP midfoot slightly increased and CoPP forefoot, M-L SPARC and A-P SPARC decreased (all *P*<.001). Small but significant age effects revealed decreased CoPP hindfoot (*P*=.04), increased CoPP forefoot (*P*=.01) and reduced M-L SPARC (*P*<.001) with increasing age. Details on linear mixed models and the resulting regression equations can be found in appendix B.

5. Discussion

This study aimed to investigate foot function by characterizing the foot-floor contact pattern in a group of people with DS compared to a group of typically developing children and able-bodied adults. Six parameters were selected to evaluate the progression, length and smoothness of the CoP trajectories on the plantar surface of the foot. About half of the participants with DS did not consistently initiate their step with a heel strike. The relative duration of CoP progression in non-heel strikes was larger on the forefoot and lower on the hindfoot, as was expected since most of the non-heel strikes were forefoot strikes. The typically v shaped CoP trajectory of these non-heel strikes was reflected in longer path lengths and decreased antero-posterior smoothness. The DS_inconsistent subgroup also showed deviant CoP trajectories when only heel strikes were compared with DS_consistent and control group. More specifically, the CoP progression significantly differed, revealing a quick transition of the CoP from hind- to midfoot region in DS_inconsistent. Contrary to our hypothesis, DS participants did not perform heel strikes with different path lengths or smoothness compared to the control group. These results showed that the foot-floor contact pattern was significantly different in patients who were unable to consistently perform heel strikes. Patients with impaired foot function can be distinguished based on foot strike pattern and deviant CoP trajectories.

In previous research on typically developing children, mid- and forefoot strikes have been frequently observed early after the onset of independent walking. The foot strike patterns normalized to heel strikes during the first year of walking experience and the gait line appeared smoother with increasing age (Bertsch, Unger, Winkelmann, & Rosenbaum, 2004; Gallahue & Ozmun, 1998; Hallemans, De Clercq, Dongen, & Aerts, 2006). In DS, not only a later onset of independent walking but also a persisting delay in overall motor development is observed (Verheyen, Verbecque, et al. 2019), which could contribute to immature foot strike patterns. These observations might indicate immaturity of gait in children and adults

with DS. This hypothesis is supported by the findings of significant age effects on CoP trajectory parameters and younger age in the DS_inconsistent group.

Even when participants with DS did perform heel strikes, it is likely that increased time during which CoP was situated on the midfoot (increased CoPP midfoot) bears the functional significance of a quest for more stability or may reflect altered muscle function. Stability issues during gait are in line with previous research suggesting that atypical crouch gait and increased step width were compensation strategies to increase stability by lowering the centre of mass and widening the base of support (Di Marco et al. 2019). Impaired motor control or muscle strength may cause the incapacity to slow down the forward motion of the tibia (Gage 1993) which would result in a quick transition of the CoP from hind- to midfoot. This may be reflected in kinematic deviations previously described in this population, specifically early and increased ankle dorsiflexion (Di Marco et al. 2019) and might contribute to crouch gait (Rodda et al. 2012; Di Marco et al. 2019; Gage 1993). Pathophysiologic findings in DS suggest that motor control is often disturbed owing to central nervous disorders (Catterall 2018; Darra et al. 2019) and possibly peripheral neuropathy (Gitiaux et al. 2016). Clear muscle weakness is not reported, but studies evaluating strength are lacking (Rodda et al. 2012). Future studies should investigate the link between CoP progression, clinical findings and the gait pattern.

Besides stability, strength or control issues, also malalignment of the foot may affect the excursion of the CoP (Fuller 1999). Deviating static foot postures were observed in 65% of the participants with DS, mostly pronated feet (planovalgus). Foot morphology could directly affect the CoP trajectory and may also be linked to abnormal foot strike patterns, as 77% of the participants with pronated feet also performed non-heel strikes. Further investigation of the dynamic behaviour of these deviations during gait and the influence of supportive footwear is needed to clarify how foot morphology may contribute to gait deviations in children and adolescents with DS.

For in depth investigation of the link between CoP trajectories and the gait pattern, additional video or three dimensional gait analysis (3DGA) is required. This combination proved to be more accurate to identify regions of the foot (Giacomozzi and Stebbins 2017) and to detect the absence of a heel strike (Mudge et al. 2019). Furthermore, 3DGA provides essential information on gait patterns and should ideally be performed to assess gait in patients with DS. However, even better participant collaboration is needed to collect reliable 3DGA data and it requires advanced motion capture infrastructure (Hallemans et al. 2019). Hence, when 3DGA proves too demanding in participants with severe cognitive and behavioural

impairments, pedobarography combined with video analysis may offer a feasible alternative. The CoP trajectory may then provide insight into foot function and mechanical control to enable integrated interpretation of observed gait deviations (Jameson et al. 2008).

The results imply that people with DS may benefit from interventions that improve foot-floor contact patterns and provide stability in order to walk with a more efficient pattern. Physiotherapy with an emphasis on practicing correct foot strike patterns and improving plantar flexor muscle function could be indicated. Shoes could provide stability around ankle and foot, especially in combination with orthopaedic insoles in case of foot deformities.

Cognitive and behavioural impairments in people with DS were a limiting factor that could impact the generalizability of the results. Out of 46 eligible candidates, 15 were excluded because the minimum of three representative steps for one side was not reached owing to behavioural or cognitive limitations. It remains unclear whether these participants' foot-floor contact patterns were similar to the included participants with DS or if their exclusion resulted in an underrepresentation of severely affected patients in this study.

6. Conclusion

Half of the participants with DS showed inconsistency in the type of foot-floor contact (heel strikes and non-heel strikes). Even when participants in this subgroup performed heel strikes, their CoP progression pattern differed from typically developing controls, more specifically by a reduced duration of CoP under the heel and a prolonged duration under the midfoot.

7. Acknowledgements and funding

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Appendix A: Correlation matrix calculation

As long as participants cooperation was ensured, trials were repeated until at least six successful steps per side were collected. Due to behavioral difficulties, all 'clean' steps on the platform were collected, even steps that were less representative for the participants usual gait pattern. Less representative altered walking patterns such as playful 'funny' walking, pauses on the force plate or direction changes, would be reflected in the 2D pressure image of the footprint. Steps that were considered as the most representative were identified in a standardized manner. Hereto, custom made MATLAB® scripts (R2018a, The Mathworks Inc, Natick, MA, US) were used to calculate correlations between all pressure distribution images within each participant. For each side, the three footprints with the highest correlation among each other were selected for further analysis.

Each footprint was originally exported in ASCII-files, containing values measured by each sensor identified via row and columns coordinates describing the whole device. The area containing the footprint (region of interest, ROI) was then extracted without ignoring null areas possibly associated with cavus feet. ROI boundaries were identified as the first and last non-null rows and columns of the device-matrix.

Different footprints could have been differently oriented with respect to the device reference frame due to: 1) Walking direction not perfectly longitudinal to the device; 2) Altered walking pattern. Different walking direction would only affect the footprint orientation, whereas an altered walking pattern may additionally affect the pressure values. Extracted ROIs were therefore reoriented by first fitting an ellipse containing the whole ROI, and then using the angle between the main axis of inertia of this ellipse and the horizontal axis to rotate the footprint.

The reoriented images, i.e. the pressure value matrices, are then pairwise compared via the CORR2 Matlab function. This function computes the Pearson's correlation coefficient (*r*) between two matrices **"A"** and **"B"** of the same dimensions (in the case of images **"A"** and **"B"** are two matrices of pixel intensity). This 2D-*r* is calculated similarly to the 1D case, and specifically:

$$r = \frac{\sum_i \sum_j (a_{ij} - \bar{a})(b_{ij} - \bar{b})}{\sqrt{\left[\sum_i \sum_j (a_{ij} - \bar{a})^2\right]\left[\sum_i \sum_j (b_{ij} - \bar{b})^2\right]}}$$

Where:

- a_{ij} is the element of the matrix **A** at row i and column j;
- b_{ij} is the element of the matrix **B** at row i and column j;
- $\bar{\bar{a}}$ and $\bar{\bar{b}}$ are the grand average (i.e., over rows and columns) of the element values of the matrices **A** and **B**, respectively.

The function CORR2 calculates the difference between each *ij*-th value in **"A"** and **"B"** and the grand average of those whole matrices, with respect to the difference of each individual matrix.

As a result of the comparison of n images, a symmetric square *n*-order correlation matrix is obtained as output of the algorithm (Figure A), with each *xy*-th element being the Pearson's coefficient *r* calculated comparing the *x* and *y* images

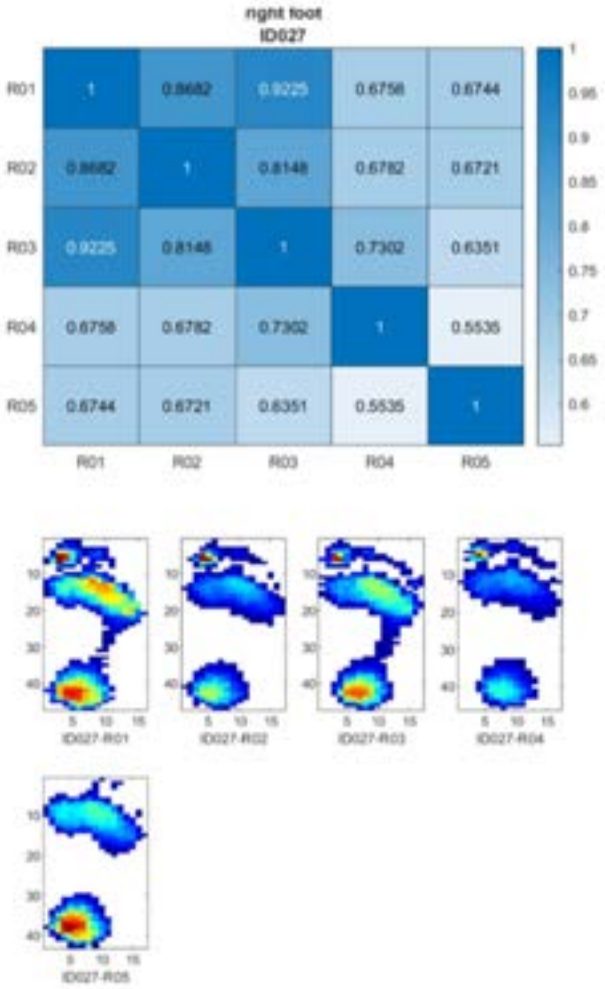

Figure A1. An example of correlation matrix (above) obtained with the algorithm used to select the footprints (below). The main diagonal displays ones as the algorithm compares the i-th image with the image itself.

Appendix B: Linear mixed models analysis

The difference in outcome between i) heel strikes and non-heel strikes and ii) Dravet Syndrome (DS) and control group, accounting for age and total contact time (TCT), was modelled using linear mixed models (LMM). LMM are a type of regression models that support the analysis of non-independent data. Where traditional regression and ANOVA techniques assume independent observations, LMM can account for the relatedness between observations by including random effect terms. These terms describe the dependence structure of the observations and the standard errors of the parameter estimates are adjusted accordingly.

In this particular case, multiple measurements were included per individual participant. Measurements within one participant were not independent. In addition, participants were repeatedly tested for the left side and the right side. Observations within one side were not independent either. This latter dependence was nested within the within-participant dependence.

Hence, LMM contain two types of independent variables. The variables for which the effect is to be tested (usually the research question of the experiment) are referred to as "fixed effects". In the current study they included group, age and TCT. The variables describing the dependence between observations are referred to as "random effects". In this study they included individual and side.

Two linear mixed models were fitted: the first one (Stage 1) within DS, with the fixed effect for group describing heel strikes versus non-heel strikes, and the second one (Stage 2) within heel strikes, with the fixed effect for group describing DS versus control. In addition to the fixed effect for group, we added the covariates age, total contact time (TCT) and side as fixed effects. Since TCT is directly related to walking velocity, this factor was added to account for velocity-dependent differences. Random effects for subject and side, nested within subject, were entered to account for non-independence of observations within individuals and sides. Significance of the fixed effects was tested using a likelihood ratio test.

For i = 1 … n, with n the number of subjects and j = 1 … m, with m the number of trials, the outcome parameter Y_{ij} can be estimated using the following formula:

$$Y_{ij} = (\beta_0 + b_i) + \beta_1 * group_i + \beta_2 * age_i + \beta_3 * TCT_{ij} + \beta_4 * side_{ij} + \varepsilon_{ij}$$

with β_0 the population intercept, bi the individuals random deviation from the intercept, β_1 the fixed effect of group (with β_{1_c} the coefficient for the DS_consistent subgroup and β_{1_i} for the DS_inconsistent subgroup), β_2 the fixed effect of age, β_3 the fixed effect of total contact time,

β_4 the fixed effect of side and εij the residuals. In stage 1, group was defined as heel strike (0) or non-heel strike (1). In stage 2, group was defined as control (0) or Dravet Syndrome (1). The estimated coefficients with their standard error (SE) and the *P*-value of the likelihood ratio test (χ^2) can be found in table B1 and LMM predictions are plotted for TCT in figures B1 and B2.

For two parameters (CoPP hindfoot and CoPP midfoot), a significant fixed effect for the variable 'group' existed. Post-hoc pairwise comparison with Bonferroni correction was performed calculating estimated marginal means, in order to assess the significance of the differences between pairs of subgroups. Results of the post hoc tests are reported in table B2.

Table B1

Results of the linear mixed models and likelihood ratio test per parameter:

	Stage 1					**Stage 2**					
	Non-heel strikes versus heel strikes (DS only)					**DS subgroups versus control (heel strikes only)**					
	β_0	β_1	β_2	β_3	β_4	β_0	β_{1_c}	β_{1_i}	β_2	β_3	β_4
	Y_{ij} = CoPP hindfoot										
Estimate	0.091	-0.115	-0.002	1.37E-04	-0.003	0.181	-0.019	-0.075	-0.002	8,24E-5	-0,001
SE	0.049	0.020	0.002	6.27E-05	0.013	0.038	0.020	0.021	0.001	5,82E-5	0,009
***P*-value**		<.001*	.22	.03*	.83		.002*		.04*	.17	.92
	Y_{ij} = CoPP midfoot										
Estimate	0.155	0.006	-0.002	2.50E-04	0.008	0.106	0.027	0.100	-0.001	2,27E-4	-0,005
SE	0.070	0.027	0.003	8.21E-05	0.019	0.043	0.023	0.024	0.001	6,65E-5	0,011
***P*-value**		.81	.37	<.001*	.67		<.001*		.30	<.001*	.63
	Y_{ij} = CoPP forefoot										
Estimate	0.754	0.089	0.003	-3.91E-04	-0.001	0.697	-0.015	-0.035	0.003	-3,04E-4	0,011
SE	0.065	0.026	0.002	7.95E-05	0.020	0.045	0.025	0.026	0.001	6,60E-5	0,011
***P*-value**		<.001*	.13	<.001*	.98		.38		.01*	<.001*	.32
	Y_{ij} = Length Ratio										
Estimate	0.869	0.189	-0.004	2.05E-04	0.024	0.966	-0.010	-0.038	-0.002	7,08E-5	0,007
SE	0.074	0.030	0.002	9.50E-05	0.021	0.037	0.025	0.026	0.001	4,82E-5	0,008
***P*-value**		<.001*	.11	.03*	.24		.32		.13	.14	.39
	Y_{ij} = M-L SPARC										
Estimate	-1.331	-0.500	-0.038	-3.38E-03	0.036	-1,668	0.030	-0.008	-0.047	-0.003	0,07
SE	0.651	0.273	0.021	8.19E-04	0.218	0.491	0.252	0.268	0.014	0.001	0,132
***P*-value**		.08	.07	<.001*	.86		.98		<.001*	<.001*	.60
	Y_{ij} = A-P SPARC										
Estimate	-1.189	-1.336	0.009	-2.84E-03	-0.027	-1,067	-0.064	-0.295	0.003	-0.003	0,078
SE	0.416	0.160	0.016	4.94E-04	0.124	0.242	0.148	0.158	0.008	3,46E-4	0,056
***P*-value**		<.001*	.56	<.001*	.82		.19		.72	<.001*	0.16

* significant after Benjamini-Hochberg correction with false discovery rate 0.05; DE, Dravet Syndrome; SE, Standard Error; CoPP, center of pressure progression; SPARC, Spectral arc length; M-L, medio-lateral; A-P, antero-posterior

Table B2

Results of the post hoc estimated marginal means analysis: pairwise differences of the variable 'group'

	Control versus DS_ consistent	Control versus DS_ inconsistent	DS_consistent versus DS_ inconsistent
	Y_{ij} = CoPP hindfoot		
Estimate	0.019	0.075	0.056
SE	0.020	0.021	0.024
***P*-value**	1.00	.003*	.08
	Y_{ij} = CoPP midfoot		
Estimate	-0.027	-0.100	-0.074
SE	0.023	0.025	0.028
***P*-value**	.77	<.001*	.03

*significant at α=.05 with Bonferroni correction; DS, Dravet syndrome subgroup of patients that always performed heel strikes (consistent) or patients that switched between heel strikes and non-heel strikes (inconsistent); SE, Standard Error; CoPP, center of pressure progression.

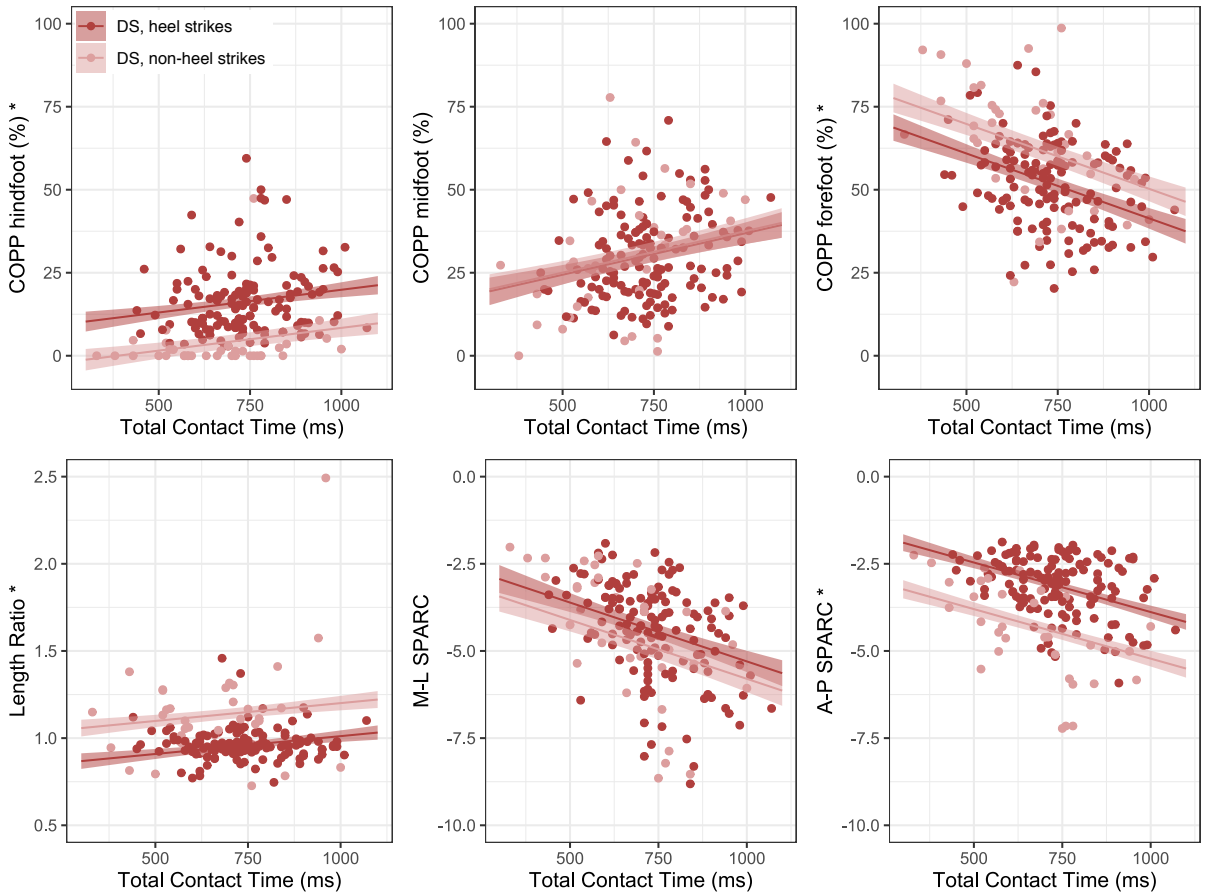

Figure B1. Linear mixed model predictions for total contact time within the Dravet Syndrome (DS) group. * Parameter with significant difference between heel strikes (dark red) and non-heel strikes (light red); CoPP, center of pressure progression; SPARC, Spectral arc length; M-L, medio-lateral; A-P, antero-posterior.

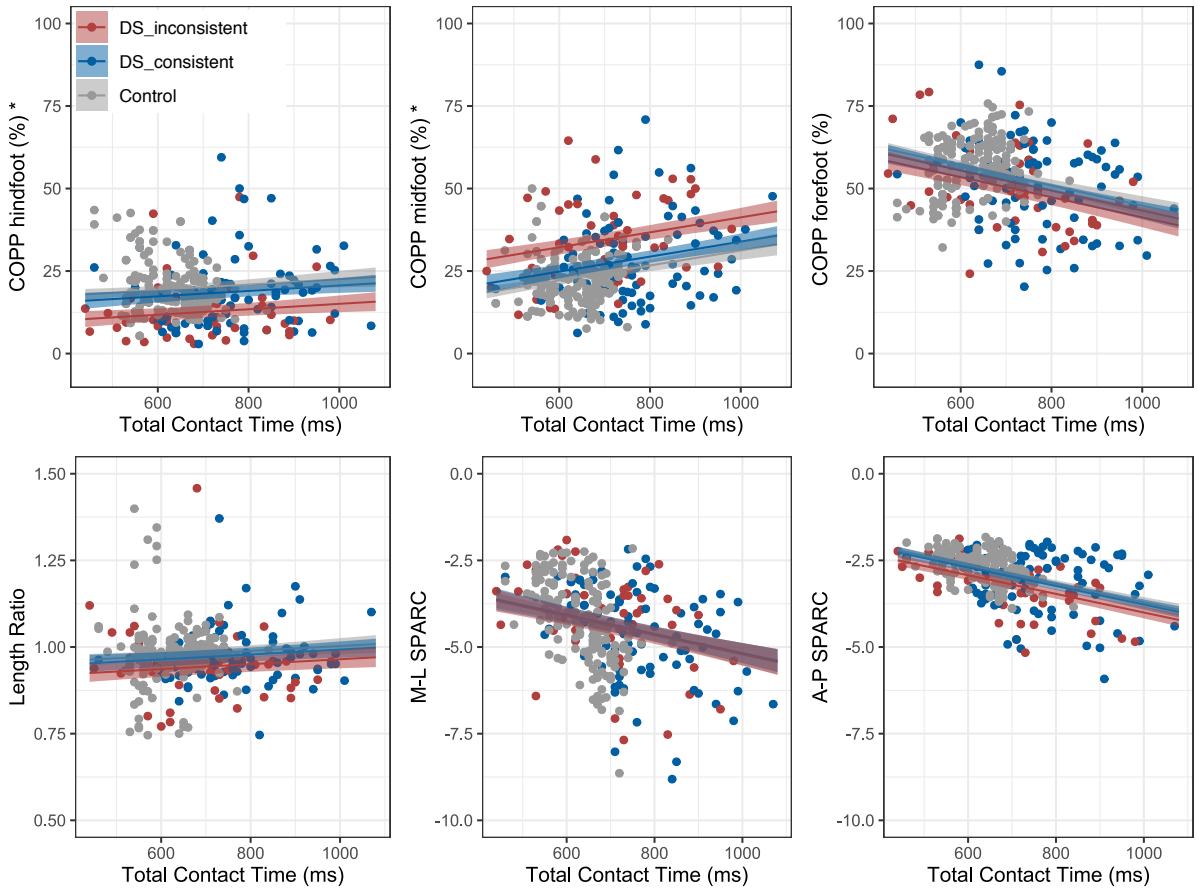

Figure B2. Linear mixed model predictions for total contact time within heel strikes. * = Parameter with significant difference between heel strikes of the DS subgroups (dark red and blue) and control (grey) group. CoPP, center of pressure progression; SPARC, Spectral arc length; M-L, medio-lateral; A-P, antero-posterior.

Chapter 5

Strength measurements in patients with Dravet Syndrome

Chapter 5

Strength measurements in patients with Dravet Syndrome

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1. Abstract

Background: Dravet Syndrome (DS) is a developmental and epileptic encephalopathy, characterized by drug resistant infantile onset seizures and cognitive and motor impairment. Walking problems progressively occur and crouch gait is frequently observed. Muscle weakness is hypothesized as contributing impairment. Yet, so far, no studies have performed strength measurements in patients with DS, most likely due to cognitive impairment.

Objective: To determine the feasibility and validity of strength measurements in the framework of gait analysis and to outline strength problems in patients with DS.

Methods and Procedures: Manual muscle testing, dynamometry (hand grip strength and handheld dynamometry) and functional tests (underarm throwing, standing long jump, sit-to-stand, stair climbing) were performed in 46 patients with DS. Results were compared to age-related reference values from literature. The validity of functional tests was investigated by calculating partial correlations with dynamometry, while controlling for height and BMI.

Outcomes and Results: Forty one percent (19/46) of the patients (aged 5.2-24.8 years, median: 15.8 years) accomplished all measurements and scored generally below the fifth percentile of norm values. The remaining 59% (27/46) was not able to complete all strength assessment due to cognitive, behavioural and motor difficulties. Handheld dynamometry seemed most sensitive and specific to detect isolated muscle strength. Validity of the functional tests was controversial, as motor proficiency, balance and coordination may interfere.

Conclusions and Implications: Although measuring strength in patients with DS was challenging in the context of gait analysis, decreased muscle strength was observed in patients that could perform strength measurements. Handheld dynamometry is preferred over functional tests for future investigations of muscle strength and its interference with gait are required for better understanding of walking problems.

2. Introduction

Dravet Syndrome (DS) is a developmental and epileptic encephalopathy, primarily caused by mutations in the neuronal sodium voltage-gated channel type 1 alpha subunit encoding gene (*SCN1A*) (Claes et al. 2001). The syndrome is characterized by drug resistant infantile onset seizures with cognitive impairment and progressive motor problems (Dravet 2011; Scheffer et al. 2017). Walking difficulties become a major concern around adolescence,

making many patients lean on others or use a wheelchair for longer distances (Rodda et al. 2012; Villas, Meskis, and Goodliffe 2017). The gait pattern is described as unstable and inefficient, with crouch gait observed in about 50% of the patients (Wyers, Van de Walle, Hoornweg, et al. 2019; Di Marco et al. 2019). Instrumented three-dimensional gait analysis (3DGA) has only recently been performed in this population (Di Marco et al. 2019) but is necessary for in-depth understanding of the nature of gait deviations (Gage 1993; Baker et al. 2016; Brunner and Rutz 2013). To enhance clinical interpretation of the results, physical examination is generally expected to be part of 3DGA (Baker et al. 2016; Desloovere et al. 2006). Assessment of muscle strength is a key element of physical examination, since muscle weakness is considered to be an important contributor to gait deviations such as crouch gait (Damiano and Dodd 2002; Brunner and Rutz 2013; Thompson et al. 2011; van der Krogt, Delp, and Schwartz 2012; Desloovere et al. 2006). Previous studies hypothesized a contribution of muscle weakness to gait deviations in DS, but were not able to perform strength measurements, due to low cognitive abilities of the participants (Rodda et al. 2012; Rilstone et al. 2012).

Various methods to measure strength in paediatric populations are documented in literature (Bohannon 2019). During *manual muscle testing* (MMT), an assessor grades (0-5) the contraction against a manually administered resistance (Hislop and Montgomery 2007). Although this method is widely performed in clinical practice as a quick assessment of specific muscle groups, MMT largely depends on evaluator's experience and its sensitivity to detect change over time is low (Bohannon 2005; Mahony et al. 2009; S. Schwartz et al. 1992; Beasly and Beasley 1956; Escolar et al. 2001). *Dynamometry* objectively quantifies muscle strength and can be performed with relatively cheap and accessible instruments known as hand-held dynamometers (HHD) and hand grip strength devices (HGS). In HHD, the participant performs a maximum voluntary isometric contraction (MVIC) against a force transducer held perpendicular to the moving limb. Compared to the gold standard isokinetic testing, HHD can be considered a valid and reliable instrument for muscle strength assessment in a clinical setting (Stark et al. 2011). In HGS, the participant holds the dynamometer to measure grip strength, which may be an indicator of total muscle strength (Wind et al. 2010). As an alternative that is more motivating and closer to children's daily activities, *functional tests* are frequently used to estimate muscle strength. Aertssen et al. (2016) developed and validated the Functional Strength Measurement test battery (FSM), by selecting activities with strength as an important factor for successful performance, but low coordination requirements (Aertssen, Ferguson, and Smits-Engelsman 2016). While HHD

measures the isometric contraction of a muscle group around a single joint, functional tests indirectly estimate strength of multiple muscles combined around multiple joints. Concurrent validity of the FSM with HHD was therefore moderate in typically developing (TD) children (Aertssen, Ferguson, and Smits-Engelsman 2016).

Reliability and validity of the above mentioned methods are investigated in populations of children and adolescents with a TD (van den Beld et al. 2006a; Aertssen, Ferguson, and Smits-Engelsman 2016; van den Beld et al. 2006b), neurologic and orthopaedic disorders (Mahony et al. 2009; Verschuren et al. 2008; Aertssen et al. 2019; van den Beld et al. 2011; Escolar et al. 2001) and intellectual disabilities (Aertssen, Steenbergen, and Smits-Engelsman 2018; Wouters et al. 2017; Wuang et al. 2013). However, owing to the specific combination of motor and cognitive impairments, behavioural difficulties and seizures triggered by temperature rise and physical exercise (Dravet 2011), it remains unclear how feasible and valid the different tests are in a population with DS.

For thorough understanding of gait deviations and to enable appropriate interventions, insight in muscle strength in patients with DS is needed. However, no studies on muscle strength in DS have been reported so far. Therefore, the aim of this study is to determine how feasible strength measurements are in the framework of gait analysis in patients with DS and to detect strength problems. More specifically, we will attempt to perform *MMT*, *dynamometry* and *functional tests* in a group of patients with DS. We expect that not all participants will be able to perform the measurements. Comparison to normative reference values will reveal whether possible weakness can be detected. To investigate if functional tests offer a valid alternative to isometric strength tests, concurrent validity of the FSM compared to dynamometry will be assessed using correlation analysis.

3. Methods

3.1 Study design and setting

This cross-sectional study was part of a project on gait disorders in patients with DS registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03857451) and approved by the ethics committees of the Antwerp and Leuven University Hospitals (Belgian Registration Number B300201627079). Participants attended gait analysis sessions including physical examination of joint range of motion, alignment, muscle length and strength, at annual follow up at the Multidisciplinary Motor Centre Antwerp (M²OCEAN). The strength assessment

protocol for the current study was performed as part of the physical examination between October 2018 and November 2019.

3.2 Participants

Patients diagnosed with DS and a confirmed *SCN1A* mutation were recruited through the department of child neurology at the Antwerp University Hospital and the parent organization of the Netherlands and Flanders 'Stichting Dravetsyndroom Nederland/Vlaanderen'. Exclusion criteria were the occurrence of a severe epileptic seizure within 24 hours before the assessment and comorbidities of other neurological and/or orthopaedic disorders not related to DS.

Table 1
Standardized positions for the muscle groups tested using hand-held dynamometry.

Muscle group	Participant position	Device	Device position
Hand grip strength	Sitting, shoulder adducted, elbow 90° flexed	Jamar ®	In hand, second position*
Elbow flexors	Supine, shoulder adducted, elbow 90° flexed, forearm supinated	MicroFET ®	Flexor surface of forearm, just proximal to wrist
Elbow extensors	Supine, shoulder adducted, elbow 90° flexed, forearm supinated	MicroFET ®	Extensor surface of forearm, just proximal to wrist
Hip flexor	Supine, hip 90° flexed, knee fully relaxed, foot not supported	MicroFET ®	Anterior surface of thigh, just proximal to knee
Knee extensors	Sitting, knee 90° flexed	MicroFET ®	Anterior surface of shank, just proximal to knee

*adapted to first or third position if not comfortable for participant

3.3 Data collection

3.3.1 Demographics

Body mass (kg) and height (mm) were measured using a digital scale with stadiometer. Body mass index (BMI) and BMI-for-age z-scores were calculated using WHO growth references in R (v 4.0.0, package 'anthro' and macro 'WHO2007', R Foundation, Vienna, Austria). Scores were classified as 'underweight', 'normal', 'overweight' or 'obese' according to De Onis et al. (2010) (De Onis and Lobstein 2010). Dominant sides for upper (writing) and lower (kicking a

ball) limb were indicated by the parents. Levels of intellectual disability (ID) were estimated by the treating physician as mild, moderate or severe and supported by cognitive test scores if available (Greenspan and Woods 2014).

3.3.2 Manual muscle testing

Knee extensor muscle strength (grade 0-5) was assessed by manual muscle testing according to Daniels and Wortingham's technique (Hislop and Montgomery 2007). As all patients were able to move the limb against gravity, the test was performed with the participant in sitting position. The 'make' method was used: the assessor applied resistance against concentric muscle contraction with the hand placed distally on the tibia. The amount of resistance was graded from 3+ (minimal) to 5 (maximal).

3.3.3 Dynamometry

The HGS (kg) was assessed using a Jamar® hydraulic hand dynamometer (Patterson Medical, IL, USA) in standardized position (table 1) adopted from Ploegmakers et al. 2013 with the handle in second position unless this was not comfortable for the participant (Bohannon, Wang, and Noonan 2019; Ploegmakers et al. 2013). Four muscle groups' MVIC's (Newton) were measured using a MicroFET2® hand-held dynamometer (Hoggan Scientific, UT, USA). More specifically, elbow flexors, elbow extensors, hip flexors and knee extensors were tested in standardized positions with the device most distally on the moving limb, adopted from Beenakker et al. (2001) (Beenakker et al. 2001) (table 1). The 'make' method was used: the assessor held the device stationary and asked the participant to push as hard as possible against the force transducer. After giving the 'Ready? Start!' signal, the assessor counted out loud to five in order to encourage the participant to gradually achieve maximum force.

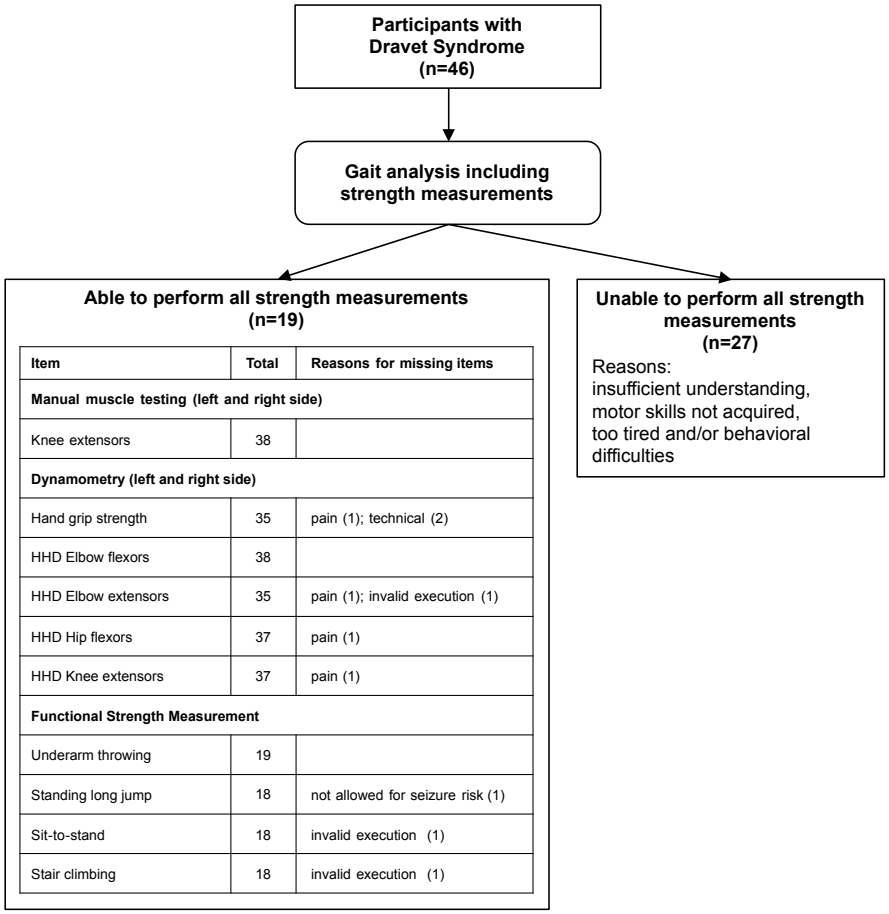
3.3.4 Functional tests

Out of the original eight items of the FSM (Aertssen, Ferguson, and Smits-Engelsman 2016), only four were performed in order to reduce protocol duration: standing long jump (SLJ, cm), underarm throwing (UT, cm), stair climbing (SC, number of steps during 30 sec) and sit to stand (STS, number of repetitions during 30 sec). All tests were performed according to the FSM protocol by Aertssen and Smits-Engelsman (2012) (Aertssen and Smits-Engelsman 2012) with three adaptations. First, in order to reduce protocol duration and physical

exertion, the warm-up protocol and practice trials were not performed. Second, for safety reasons, alternating steps was not required and slight arm support was allowed for SC. Third, to assure correct performance of STS, participants had to fold their hands during the performance and touch a drawing on the wall while standing.

3.4 Procedure

Measurements were executed in the order mentioned above. Two trials per side for dynamometry and three trials for FSM were performed, starting from the first correct execution. The highest value was used for analysis. In order to prevent fatigue, STS and SC were only performed once. All test were performed by the same assessor (MSc, physiotherapist). Verbal encouragement was given. Total duration of the strength assessments was around 30 minutes, influenced by the patient's behaviour and understanding of the tasks. Patients who were unable to correctly perform all measurements, were omitted from further analysis. Patients who were able to perform tests in all three categories, but could exceptionally not complete specific items (e.g. pain because of wound on location of HHD device, execution interrupted before 30 sec were complete) were retained as 'able to perform all strength measurements' (figure 1). Observations on challenges or reasons of invalid performance were noted.



Item	Total	Reasons for missing items
Manual muscle testing (left and right side)		
Knee extensors	38	
Dynamometry (left and right side)		
Hand grip strength	35	pain (1); technical (2)
HHD Elbow flexors	38	
HHD Elbow extensors	35	pain (1); invalid execution (1)
HHD Hip flexors	37	pain (1)
HHD Knee extensors	37	pain (1)
Functional Strength Measurement		
Underarm throwing	19	
Standing long jump	18	not allowed for seizure risk (1)
Sit-to-stand	18	invalid execution (1)
Stair climbing	18	invalid execution (1)

Figure 1: Data collection procedure. All participants performed strength measurements after gait analysis. Patients who were unable to perform all strength measurements were omitted from further analysis. Reasons for omission and for missing items in further analysis are reported. HHD, handheld dynamometry

3.5 Statistical analyses.

Strength measurement outcomes were plotted against available age-related reference values (5th, 50th and 95th percentile) available in literature: HGS paediatric values by Ploegmakers et al (2013) (Ploegmakers et al. 2013) and adult values by Peters et al. 2011 (Peters et al. 2011), HHD paediatric by Beenakker et al. (2001) (Beenakker et al. 2001) and adult by Douma et al. (2014) (Douma et al. 2014) and FSM paediatric by Aertssen and Smits-Engelsman (2012) (Aertssen and Smits-Engelsman 2012).

Visual inspection and formal tests (Shapiro-Wilk) highlighted normal distribution of the data. To test the hypothesis that FSM validly measured muscle strength, Pearson correlation coefficients were calculated between FSM and dynamometry items. As there was a wide age range and heterogeneity in body composition, confounding effects of height and BMI were expected. Therefore, partial correlations were calculated between FSM and dynamometry items, controlling for height and BMI. Additionally, Pearson and partial correlations were also calculated between HGS and the four other dynamometry items, to confirm if HGS was an indicator of total muscle strength. Since a small number of missing values occurred, complete case analysis was used. All statistical analyses were performed in IBM SPSS® software (v26.0, IBM Corp, Armonk, NY, US)

Table 2

Characteristics of patients able and unable to complete strength assessment.

	Complete strength assessment (n = 19)	Unable to complete strength assessment (n = 27)
Age		
3-4 years	0 (0%)	5 (19%)
5-7 years	4 (21%)	8 (30%)
8-11 years	4 (21%)	6 (22%)
12-17 years	6 (32%)	3 (11%)
18-26 years	5 (26%)	5 (19%)

	Complete strength assessment (n = 19)	Unable to complete strength assessment (n = 27)
Sex		
Male	11 (42%)	13 (52%)
Female	8 (58%)	14 (48%)
BMI classification		
Underweight	6 (32%)	5 (19%)
Normal	7 (37%)	17 (63%)
Overweight	5 (26%)	5 (19%)
Obese	1 (5%)	0 (0%)
ID level		
Mild	8 (42%)	5 (19%)
Moderate	8 (42%)	9 (33%)
Severe	3 (16%)	13 (48%)

BMI, body mass index; ID, intellectual disability

4. Results

Out of 46 participants, 19 patients (19/46, 41%) with DS aged 5.2 to 24.8 years (median 15.8 years) were able to complete all strength measurements (figure 1 and table 2). Twenty-seven patients (27/46, 59%) aged 3.0 to 26.1 years (median 8.4 years) were not able to complete all strength assessments due to a combination of disturbed cognitive functioning, motor skills and behaviour. More specifically, they did not understand the instructions, were not skilled to jump or throw, were too tired and/or not willing to cooperate. No seizures occurred during the assessments. Younger age and lower levels of ID were more frequent in participants unable to complete the assessments, while gender and BMI were evenly distributed (table 2).

When patients were able to perform all tests, correct execution still proved to be challenging. Ten items were missing, merely owing to circumstances than patient ability (figure 1). We observed difficulties to perform selective movements during HHD and balance problems during FSM. Frequent observations per test item are presented in table 3.

Strength measurement outcomes of patients with DS and reference values of TD children and, if available, adults are presented in table 2. All tests showed poor strength in patients with DS. Even adolescents and young adults performed below the fifth percentile of TD children. This trend was observed in analytical as well as functional strength measurements, with HHD elbow extension and FSM UT as exceptions.

Significant Pearson correlations between FSM and dynamometry were only found for UT. Pearson correlations between HGS and the four HHD items were all significant. When controlling for height and BMI, partial correlations between UT and dynamometry were only significant for elbow flexors (both sides) and extensors (dominant side). Other significant partial correlations were found for STS with elbow flexors (both sides), elbow extensors and HGS (dominant side), and for HGS with elbow flexors and knee extensor (dominant side). The significant partial correlation coefficients ranged from .57 to .73 (table 4).

Table 3

Frequent observations of the execution and challenges for the different test items in patients able and unable to complete strength assessment. HHD, hand-held-dynamometry

Test item	Frequent observations	
	Complete strength assessment (n = 19)	**Unable to complete strength assessment (n = 27)**
Manual muscle testing		
MMT Knee extensors	Participants tended to combine with hip flexion and/or backward trunk lean	Not cooperative;
		Did not understand the instruction to move against resistance
Dynamometry		
Hand grip strength	Device was heavy for small children;	Not cooperative;
	Participants wanted to turn device inwards to look on scale	Did not understand the instruction to squeeze
HHD Elbow flexors	None	Not cooperative;
		Did not understand the instructions for correct execution
HHD Elbow extensors	Participants tended to combine with forearm pronation and/or shoulder anteflexion	Not cooperative;
		Did not understand the instructions for correct execution
HHD Hip flexors	None	Not cooperative;
		Did not understand the instructions for correct execution

Test item	Frequent observations	
	Complete strength assessment (n = 19)	**Unable to complete strength assessment (n = 27)**
HHD Knee extensors	Participants tended to combine with hip extension	Not cooperative;
		Did not understand the instructions for correct execution
Functional Strength Measurement		
Underarm throwing	Loss of balance after throwing.	Not cooperative;
		Did not understand the instructions for correct execution: overarm or side throwing;
		Did not understand “as far as possible”
Standing long jump	Loss of balance after landing;	Not cooperative;
	Difficulties jumping and landing with both feet simultaneously	Not able to jump;
		Did not understand the instructions for correct execution: not standing still before jump;
		Did not understand “as far as possible”
Sit-to-stand	Participants tended to lift feet up when seated	Not cooperative;
		Did not understand “as many as possible”: abnormally slow or did not persevere for 30 sec
Stair climbing	Alternating steps was not required;	Not cooperative;
	Slight arm support for safety was allowed	Required more help than slight support;
		Did not understand “as many as possible”: abnormally slow or did not persevere for 30 sec

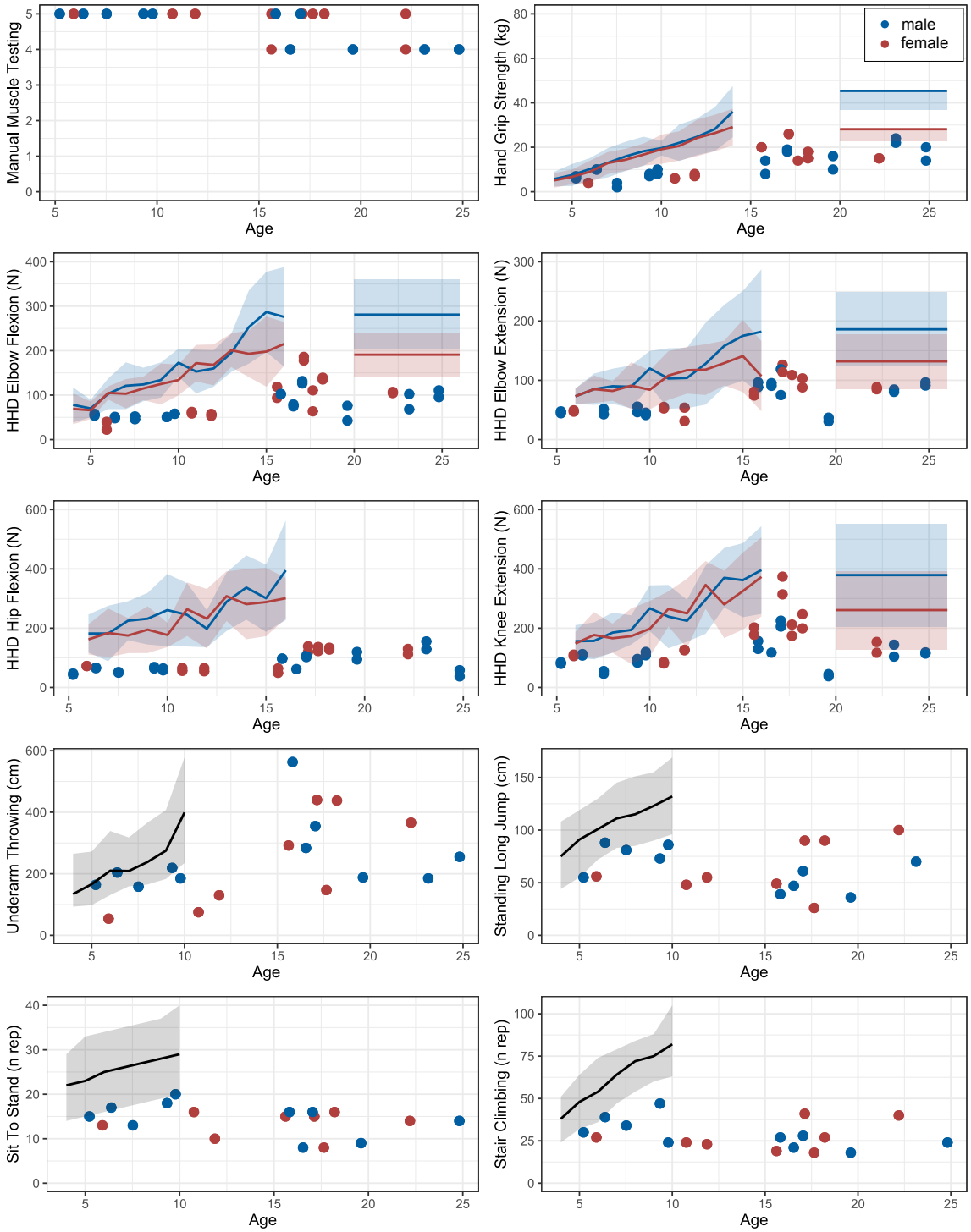


Figure 2. Strength of participants (n=19) with Dravet Syndrome compared to reference values. Lines represent P50 and shaded areas P5 to P95 of age-related reference values in typically developing children and adults, by Ploegmakers et al (2013), Peters et al. 2011, Beenakker et al. (2001), Douma et al. (2014), and Aertssen and Smits-Engelsman (2012). Red colours stand for female participants, blue for male, grey for both sexes. HHD, hand-held dynamometry; n rep, number of repetitions

Table 4

Pearson correlations and partial correlations - controlling for height and weight - between dynamometry and functional strength measurement items

	Pearson r (P-value)					Partial correlation controlling for height and BMI (P-value)				
	UT	**SLJ**	**STS**	**SC**	**HGS**	**UT**	**SLJ**	**STS**	**SC**	**HGS**
DOMINANT SIDE (n=14)										
HGS	.76**	.25	.16	.10		.40	-.03	.64*	.09	
	(.002)	(.39)	(.57)	(.74)		(.19)	(.94)	(.02)	(.78)	
Elbow flexors	.81**	.38	.25	.22	.94**	.65*	.26	.73**	.35	.71**
	(<.001)	(.19)	(.39)	(.44)	(<.001)	(.02)	(.41)	(.008)	(.27)	(.009)
Elbow extensors	.80**	.39	.27	.32	.84**	.64*	.25	.61*	.46	.37
	(<.001)	(.17)	(.36)	(.27)	(<.001)	(.02)	(.43)	(.03)	(.13)	(.24)
Hip flexors	.73**	.39	.01	.25	.67**	.26	.52	.25	.47	-.33
	(.003)	(.17)	(.98)	(.38)	(.008)	(.42)	(.08)	(.44)	(.12)	(.29)
Knee extensors	.68**	.41	.25	.24	.88**	.44	.24	.57	.29	.65*
	(.008)	(.14)	(.38)	(.42)	(<.001)	(.16)	(.45)	(.053)	(.35)	(.02)
NON-DOMINANT SIDE (n=15)										
HGS	.58*	.16	-.04	.01		.05	.25	.44	.15	
	(.02)	(.56)	(.89)	(.96)		(.88)	(.42)	(.13)	(.62)	
Elbow flexors	.75**	.24	.01	.12	.87**	.57*	.43	.59*	.41	.33
	(.001)	(.40)	(.97)	(.67)	(<.001)	(.04)	(.14)	(.04)	(.17)	(.27)
Elbow extensors	.69**	.06	-.01	.10	.67**	.48	-.04	.34	.24	-.21
	(.005)	(.84)	(.97)	(.72)	(.006)	(.09)	(.89)	(.26)	(.42)	(.49)
Hip flexors	.56*	.13	-.27	.05	.69**	.00	.27	-.12	.23	-.14
	(.03)	(.65)	(.33)	(.87)	(.004)	(1.00)	(.37)	(.70)	(.45)	(.66)
Knee extensors	.57*	.23	.11	.12	.79**	.40	.21	.55	.25	.42
	(.03)	(.41)	(.70)	(.68)	(<.001)	(.18)	(.49)	(.051)	(.41)	(.15)

n, number of complete cases; SLJ, standing long jump; UT, underarm throw; STS sit to stand; SC, stair climbing;*P<.05; **P<.01

5. Discussion

This study aimed to determine how feasible and valid strength measurements are in the framework of gait analysis in patients with DS and to outline strength problems in patients with DS. Feasibility was low, as only 41% of the participants (19/46) were able to perform MMT, dynamometry (HGS and HHD) and FSM items (UT, SLJ, STS, SC). Muscle weakness was confirmed, with measurement outcomes generally situated below the fifth percentile of typically developing children.

The context of gait analysis increased the challenge of strength assessments. As good collaboration during gait analysis was prioritized, strength assessments were performed at the end of the session. Patients may have been tired of the demanding cooperation during gait analysis and passive clinical examination. Feasibility and performance may improve when tests are administered in an isolated context with warming up and practice time. During gait analysis sessions on the other hand, an easy-to-administer test that offers an estimation of strength, adequate to understand its interference with gait, is needed. It is not recommended to perform the complete protocol used in this study, but to select test items based on feasibility, validity and sensitivity to detect strength problems.

5.1 Feasibility

Low feasibility was expected from the clinical image of DS with cognitive, motor and behavioural problems (Battaglia et al. 2016; Dravet 2011; Brown et al. 2020; Verheyen, Verbecque, et al. 2019). Nevertheless, almost half of the participants over the age of five proved to be able to complete strength assessment. Completion rates improved slightly with age, highlighting the role of cognitive and motor development. Low cognitive functioning (Brown et al. 2020) made it hard for patients to understand the instructions of starting position, correct movement execution and restrictions of compensatory movements. Behavioural difficulties occurred (Brown et al. 2020), in most cases manifesting themselves already before strength assessment, namely when collaboration was lacking during gait analysis and passive physical examination. It was generally a combination of problems that prevented participants to perform the tests, rather than one main reason.

Although instructions of HHD were expected to be difficult to understand for patients with ID, the tactile feedback of the device against the participant's limb and the resistance of the examiner may have enhanced its feasibility. However, selective contraction of the investigated muscle group appeared challenging. It remains unclear whether this indicated

purely compensation strategies or impaired selective motor control in patients with DS. For HGS, the heaviness of the device and position of the scale was a disadvantage. More child-friendly designed dynamometers exist such as a 'bulb' type dynamometer, with acceptable reliability (Molenaar et al. 2008). Nevertheless, Jamar type hydraulic dynamometers are widely available and showed better reliability than 'bulb' type (Molenaar et al. 2008).

The FSM appeared an engaging method to assess strength, but correct execution was challenging, required more time to practice and good understanding of the instruction "as far/fast as possible". Motor deficits and developmental delays (Verheyen, Verbecque, et al. 2019) interfered with the FSM, as it was a prerequisite that participants had acquired the motor skill and were able to learn how to correctly perform the test, strongly reducing the feasibility in patients with DS.

5.2 Validity

To investigate validity, MMT, HGS and FSM were compared to HHD, as this method could serve as a reference standard for muscle strength (Stark et al. 2011). Grade four of MMT was only given to adolescents and young adults, even though HHD of the knee extensors also revealed lower scores compared to age-related norm values in younger children. It cannot be excluded that MMT overestimated strength in young participants due to its subjective character: in paediatric populations, the assessor grades relative to what they expect as a maximum examiner-imposed resistance possible for the participant's age. It has been suggested that HGS can serve as an indicator of general muscle strength (Wind et al. 2010), but partial correlations revealed that HGS could predict strength of some, but not all muscle groups. Low validity of the FSM to measure muscle strength was detected by the absence of a correlation between three items (SLJ, STS and SC) and HHD. Although HHD outcomes tended to increase with age, SLJ, STS and SC scores of adolescents with DS remained on the level of young children. Higher partial correlations were observed between UT and dynamometry of the upper limb, indicating that this item validly assessed underlying muscle strength. Balance and coordination deficits may interfere with FSM, especially SLJ and SC (Aertssen, Steenbergen, and Smits-Engelsman 2018). These findings are partly in line with previous literature. The FSM proved to be a valid assessment of muscle strength with minimal demand of balance and coordination in TD children (Aertssen, Ferguson, and Smits-Engelsman 2016), but correlated significantly with balance tests in children with mild ID (Aertssen, Steenbergen, and Smits-Engelsman 2018). Feasibility and reliability were lower in children with moderate and severe ID (Wouters et al. 2017).

5.3 Strength problems

In order to detect strength problems in DS and to assess the sensitivity of the different methods, comparison with reference values was performed. Since all included scores on MMT showed the ability to contract muscles against resistance, clear muscle weakness was not detected, suggesting that strength is only mildly decreased in patients with DS. As was expected MMT was not sensitive enough to reflect smaller variations within this range (Bohannon 2005; Mahony et al. 2009; S. Schwartz et al. 1992; Beasly and Beasley 1956). In circumstances where an assessor needs to form a quick idea of muscle strength for clinical purposes, MMT may be adequate. However, to document strength for objective analysis of its relationship with gait parameters and to detect change over time, MMT does not suffice (Bohannon 2005; Aitkens et al. 1989).

Dynamometry has a higher sensitivity to objectively detect differences with reference values. Patients with DS showed poor HGS compared to age-related norms. Comparison of HHD with norm values available in literature is complicated due to variations in devices, methods and positions of participant and examiner. A major difference was the use of the 'make' method in this study and the 'break' method in the studies by Beenakker et al. (2001) and Douma et al. (2014). We preferred the 'make' method as it was supposed to be more reliable and easier to understand for children with cognitive and neurological problems (Stratford and Balsor 1994; Verschuren et al. 2008; Damiano and Dodd 2002). However, studies that collect normative values usually prefer the 'break' method: the examiner overcomes the participant's maximum strength. The peak value is higher in 'break' tests, as eccentric muscle contractions occur at the moment the limb gives way (Bohannon 1988; Stratford and Balsor 1994). Comparison with reference values plotted on figure 2 should therefore be made with caution. Forces during 'break' test are between 1.03 and 1.6 times higher than during 'make' tests in healthy adults (Stratford and Balsor 1994; Bohannon 1988). Applying this as a correction to figure 2 would bring the observed values closer to the norm values, yet the participants would still score below average. HGS may be appropriate as an indicator of general muscle strength and enables monitoring over time and comparison with norm values. But since strength of specific lower limb muscles is of interest during gait analysis, additional information could be obtained using HHD, standardized methods and examiner experience are essential.

Comparing FSM to normative values, revealed decreased functional strength. This method also proved sensitive to detect differences with TD. These differences may not only reflect decreased muscle strength, but also impaired capacity to optimally employ muscle strength during functional tasks.

For reasons mentioned above, individual scores should be interpreted with caution. On a group level, the results suggested that muscle strength in DS is decreased compared to TD children and healthy adults. This was in line with studies in populations with ID in general, showing lower levels of physical fitness and muscle strength (Horvat, Pitetti, and Croce 1997; Gillespie 2003; Wuang et al. 2013; Wouters et al. 2017; Aertssen, Steenbergen, and Smits-Engelsman 2018), associated with gait deviations (Alyt Oppewal and Hilgenkamp 2018). It remained unclear whether reduced strength in DS solely resulted from lower levels of physical activity due to seizure risks and motor problems, or if pathophysiology of sodium channel dysfunction may have played a role (Gitiaux et al. 2016). Interventions targeting muscle strength and physical fitness may be indicated to improve gait and functional mobility in patients with DS (Damiano and Dodd 2002; Alyt Oppewal and Hilgenkamp 2018).

5.4 Limitations

This study did not investigate reliability of the measurements, which can be considered a limitation. For practical reasons, strength tests could only be performed once. In order to ensure the highest reliability, all tests were performed by the same assessor. A second limitation was poor generalizability of the results to the general population with DS, due to the low completion rates, especially in young children and more severe ID. Furthermore, comparison to normative values should ideally be performed following the exact same method and taking into account age, sex and body composition (van den Beld et al. 2011).

6. Conclusion

The feasibility of a strength measurement battery of MMT, dynamometry and FSM in the context of gait analysis was low in patients with DS due to cognitive, behavioural and motor impairments. Nearly half of the participants with a minimum age of five years were able to complete the strength assessment consisting of MMT, dynamometry and functional tests. The context of gait analysis increased the challenge of strength assessment and required an easy-to-administer test that provides a sensitive and quantitative estimate of muscle strength. These requirement were best met by HHD of specific lower limb muscles. From the FSM items, UT may assess upper limb strength and STS may predict general strength, while SLJ and SC could not validly measure muscle strength. Motor proficiency, balance and coordination might interfere with functional tests. Comparison of strength outcome to age norms, suggested decreased muscle strength in patients with DS. Future investigations of strength and its interference with gait are required for better understanding of walking problems.

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Discussion

Discussion

The overall aim of this PhD project was to characterise the main gait deviations in patients with DS through literature reviewing and empirical research using gait analysis (Figure 1).

The objective of *part I* was to establish the state-of-the-art regarding motion analysis and gait deviations in patients with ID and DS. Chapter 1 provided an overview of common gait characteristics in patients with ID and introduced gait analysis protocols with a discussion of their benefits and challenges in that population, including a case report on DS. Chapter 2 presented a comprehensive literature review on gait deviations in patients with DS.

The objective of *part II* was to document biomechanical aspects of gait in children, adolescents and young adults with DS. In chapter 3, three kinetic strategies were distinguished and corresponding gait deviations identified. In chapter 4, foot function was investigated by characterising foot floor contact patterns. Chapter 5 documented the feasibility and convenience of strength measurements to quantify strength underlying gait deviations.

Hereafter, a general discussion will synthetize the five chapters and discuss their clinical implications and directions for future research.

Figure 1. Outline of the dissertation. DS, Dravet Syndrome

1. Synthesis of the results

1.1 Part I: State-of-the-art

Part I established the state-of-the art regarding motion analysis and gait deviations in populations with ID in general (chapter 1) and with DS specifically (chapter 2). In this section, an integrated discussion will situate gait deviations in patients with DS within the broader population of patients with ID. Hereafter, the theoretical background of one specific, frequently reported gait pattern will be discussed in detail, namely that of 'crouch' gait. Furthermore, the benefits and challenges of gait analysis in patients with ID and DS are discussed based on the case report and protocol proposal from chapter 1.

1.1.1 Characteristics of gait in patients with ID and DS

Two systematic literature reviews provided an overview of previously reported studies on gait deviations in populations with ID in general (chapter 1) and with DS specifically (chapter 2). Chapter 1 showed that a moderate amount of studies, 64 in total, reported instrumented gait analysis in populations with ID, most frequently participants with Down syndrome. The main features of gait in ID as part of an underlying genetic syndrome, were reduced walking velocity and reduced step length, increased step to step variability and a gait pattern with increased flexion in the knee joint and hip joint together with decreased ranges of motion at the ankle joint during the second and third rocker. In a population with general ID, not related to a genetic syndrome, deviations were similar or milder and possibly depending on ID levels. Chapter 2 on the other hand concluded that literature on gait in DS was scarce, with nine studies in total, and mainly based on clinical observation. Crouch gait was observed in about half of the patients with DS next to a variety of other gait deviations such as parkinsonian and cerebellar gait. Other findings included abnormalities in spatiotemporal parameters and kinematics, passive knee extension deficits, skeletal malalignment and neurological signs.

An update of the literature search that was reported in chapter 2 yielded five new studies, all published between October 2018 and October 2020. Three of these studies were reported as conference abstracts resulting from the current PhD project (Wyers, Van de Walle, Verheyen, et al. 2019a; 2019b; Wyers, Verheyen, et al. 2019). One study by Darra et al. (2019) evaluated gait as part of a clinical neurologic exam in 84 adolescents and adults with DS. They reported motor impairments and gait deviations in more than half of the participants, with crouch gait observed in 28% of the participants. These deviations were significantly

associated with cognition and not with epileptic severity (Darra et al. 2019). Finally, one study by Di Marco et al. (2019) reported kinematics of gait measured during 3DGA in 52 children, adolescents and young adults with DS (Di Marco et al. 2019). This was a multi-centre study of our own research group and the NEUROMOVE-rehab group at the University of Padova and included patients from the same two cohorts described in part II of this dissertation. Walking velocity and stride length were significantly reduced and double support duration and step width increased in both cohorts. Data analyses revealed the distinction of two kinematic patterns within the gait of their participants: a gait pattern defined as 'atypical crouch' in 18/52 participants and a 'straight' pattern in the remaining 34/52 participants. To differentiate between the patterns, a previously introduced cut-off of 20° knee flexion at initial contact was used (Hoang and Reinbolt 2012). Sagittal plane kinematics of the 'straight' pattern did not differ significantly from normal gait. The 'atypical crouch' was characterized by increased hip and knee flexion during stance, combined with anterior pelvic tilt. The authors argued that the 'typical' crouch definition could not be adopted from classification studies in cerebral palsy (see section: Crouch gait). Ankle dorsiflexion and external foot progression was increased in individual patients, but not significant on group level. It remained unclear whether these patterns were two ends of the same spectrum of gait deviations or truly distinct patterns associated with specific clinical characteristics (Di Marco et al. 2019).

Findings on spatio-temporal and kinematic parameters were similar between patients with DS and the general population of syndrome-related ID. Although these populations may differ in neurologic and musculoskeletal impairments, they had cognitive impairment and developmental delay in common, suggesting that gait of patients with DS may largely reflect deficits in psychomotor development. Future studies should test if and how the prognosis of gait deviations in DS differs from general ID populations. Hereto, this project established a gait analysis dataset of patients with DS that can be compared to data from patients with ID owing to a different underlying pathology.

Studies in ID populations indeed showed that not only physical characteristics such as obesity and foot deformities interfered with gait; cognition itself also seemed to play an important role (Galli, Cimolin, Rigoldi, et al. 2014; Galli, Cimolin, Pau, et al. 2014; Cimolin et al. 2014; Galli et al. 2015). The results of Darra et al. (2019) were in line with these findings, showing that the occurrence of gait deviations in patients with DS was associated with the severity of cognitive impairments (Darra et al. 2019). This implies that evaluation and especially treatment of gait in DS should not only focus on physical characteristics, but also take cognitive impairments into account. Physical characteristics may be amenable to

treatment, for example muscle strength training, body weight control, orthotic management of foot deformities and even surgical correction of tibial torsion or planovalgus feet. The options and effectiveness of these interventions may be limited in DS due to cognitive impairment. On the other hand, intellectual disability by itself would not be the target of interventions to improve gait, but the motor learning process and the acquisition of motor skills may improve through physiotherapeutic interventions (Maïano, Hue, and April 2019).

1.1.2 Crouch gait

Chapter 2 demonstrated that gait deviations in DS were most often described as crouch gait, a pattern that occurred in about half of the population. The term 'crouch' refers to a flexed position of the stance limb. This terminology was adopted from gait classification studies in cerebral palsy, where Sutherland and Davids (1993) defined crouch as "increased knee flexion throughout the stance phase, with variable alignment in swing phase" (Sutherland and Davids 1993). Rodda et al. (2004) broadened the definition by considering the total sagittal plane pattern and not only the knee joint: "The ankle is excessively dorsiflexed throughout stance and the knee and hip are excessively flexed. The pelvis is in the normal range or tilted posteriorly" (Rodda et al. 2004). Various classification systems and cut-offs are in use to define crouch gait in cerebral palsy research (Rodda et al. 2004; Sutherland and Davids 1993; Nieuwenhuys et al. 2016; Wren, Rethlefsen, and Kay 2005; Hoang and Reinbolt 2012; Rozumalski and Schwartz 2009). This diversity in definitions leads to confusion when the term 'crouch' is adopted and used in other pathologies such as DS. Although the established definitions only concern kinematics of gait, they are also highly associated with underlying pathological mechanisms, causes and consequences that may be in particularly relevant for cerebral palsy, but not necessarily for DS (Rozumalski and Schwartz 2009; Armand, Decoulon, and Bonnefoy-Mazure 2016). Most of the articles included in chapter 2 did not specify how crouch gait was defined, but seemed to focus on knee flexion, while pelvis and ankle did not necessarily follow the definition by Rodda et al. (2004) (Rodda et al. 2004). Furthermore, the studies reported inconsistent findings on impairments related to crouch gait, such as muscle weakness, spasticity, contractures or lever arm dysfunction in patients with DS (Wyers, Van de Walle, Hoornweg, et al. 2019). Di Marco et al. (2019) argued that the crouch gait pattern in DS was 'atypical' compared to cerebral palsy, because the flexed pattern was less evident in swing and not associated with muscle contractures (Di Marco et al. 2019). This highlighted that the kinematic definitions established in populations with cerebral palsy can be applied to the gait pattern in DS, but the associated impairments and their related indications for treatment cannot automatically be adopted, since the underlying

pathophysiology differs. Studying kinematics is thus insufficient to understand how gait deviations arise and to guide treatment decisions. In part II of this dissertation, we therefore investigated biomechanical aspects underlying the observed kinematic gait deviations, more specifically, kinetic strategies, foot-floor contact patterns and muscle strength.

1.1.3 Benefits and challenges of gait analysis in patients with ID and DS

As walking problems were frequently observed, patients with DS may benefit from individual clinical gait analysis. Though the presentation of a case example of a patient with DS, chapter 1 first showed that 3DGA, even though it is challenging, could be performed and proved beneficial for the clinical follow-up of walking problems in patients with DS. The 3DGA pointed towards progressive crouch gait, which led to the prescription of ankle-foot-orthoses. Gait analysis with the orthoses documented improvement of the knee angle at initial contact but limited power generation around the ankle at push-off. The example further highlighted the need for long term follow-up to evaluate potential benefits and risks of the orthotic intervention. This case study illustrated that, despite the challenging nature of gait analysis in patients with DS, objective and quantitative data of sufficient quality could document the evolution of the gait pattern over time. Nonetheless, compromises such as a remaining artefact in the report and excluding EMG of the protocol were necessary. This case illustrated the potential added value of 3DGA to the clinical follow-up of patients with DS.

Since gait analysis is challenging in patients with ID, different measurement protocols could be considered, respecting the patients' capabilities and needs. In chapter 1, instrumented 3DGA was compared to VGA, and the strengths and weaknesses of both methods were discussed. This chapter showed that 3DGA provided the most objective and accurate assessment. However, it also highlighted challenges that may reduce reliability when used for patients with cognitive and behavioural difficulties. Through clinical experience in performing gait analysis in patients with DS it became clear that, in case of low cooperation, the burden and duration of the session could be reduced by using a lower limb model instead of a full body model, by leaving out EMG and by prioritising good kinematic data over the collection of kinetic data. This would lead to better compliance of the participant and improve the quality and representativeness of the remaining data. Nevertheless, if young patients or patients with severe behavioural difficulties are not able to sit still during preparations, if they pull markers off or cannot follow the instructions to walk in a straight line, no reliable 3DGA data can be collected. The choice of the most adequate method depends on the clinical goal or research objective. For young children and patients with severe ID and behavioural problems, VGA

may be preferred over 3DGA. If gait analysis is performed to document change over time, 3DGA could be administered at key moments to enable objective, quantitative comparison, while VGA could serve for in-between assessments to gain a general image and to quickly detect unexpected changes in between 3DGA sessions. Longitudinal research is needed to determine the most relevant key moments and the necessary frequency of 3DGA to detect changes.

1.2 Part II: Biomechanical aspects

1.2.1 Main findings

Chapter 3 showed that even though only two distinct kinematic patterns were described by Di Marco et al. 2019 (Di Marco et al. 2019), three kinetic strategies could be distinguished. Due to increased knee flexion in stance, the support moment was significantly higher in patients with DS in general, suggesting that stance limb support was disturbed. Different support strategies could be distinguished based on knee extensor moments and trunk lean. A first subgroup was characterised by a persistent knee extensor moment in stance and their gait pattern could be defined as 'uncompensated crouch gait'. A second subgroup attained an internal flexion moment at the knee while exhibiting forward trunk lean. This pattern can be considered 'compensated crouch gait', whereby the moment is normalized as a result of the trunk lean. The third subgroup attained an internal flexion moment and walked with a neutral or backward leaning trunk, with a gait pattern that only mildly deviated from normal gait. These results suggested that neuromechanical control was disturbed in patients with DS leading to an overall inefficient gait pattern, with different strategies to maintain stability.

In chapter 4, deviated foot-floor contact patterns confirmed the disturbed neuromechanical control. Half of the participants with DS did not consistently perform heel strikes at initial contact, but alternated with midfoot or forefoot contacts. The CoP trajectories were characterised by a faster progression from the hindfoot to the midfoot. This was interpreted as a quest for more stability or a sign that patients may fail to control the forward roll-over of the tibia during the second rocker. Furthermore, these results combined with the findings of chapter 3, revealed that forward displacement of the CoP may reflect an attempt to align the GRF anterior to the knee.

Decreased muscle strength could partly explain the observed gait deviations. Chapter 5 highlighted that the feasibility of strength tests in patients with DS is generally low, as less than half of the participants were able to complete analytic and functional strength

measurements. Yet, the patients showed decreased strength measured by the HHD in patients with DS compared to typically developing children and healthy adults. Although manual muscle testing graded muscle strength as good to normal, most HHD scores were below average and even below the fifth percentile of norm values, revealing that mild muscle weakness is present in patients with DS.

Integrated interpretation of the findings of part II provides insight into the mechanics, muscle function and thus neuromotor control behind gait (Winter and Eng 1995). This synthesis led to two main hypotheses that explain the observed gait deviations in patients with DS. First, the *musculoskeletal* hypothesis suggests that in DS, decreased muscle strength and lever arm dysfunction only partly explain the gait deviations. Second, the *motor control* hypothesis states that impaired neuromotor control and delayed psychomotor development underlie the neuromuscular dysfunction that leads to gait deviations.

1.2.2 Musculoskeletal hypothesis

Many impairments of the musculoskeletal system interfere with gait. *Muscle weakness* and *lever arm dysfunction* are two key attributors to gait deviations, especially in crouch gait (Gage 1993). One mechanism that clearly illustrates how these two elements interact is the plantar flexion – knee extension couple (Figure 2). In midstance, eccentric contraction of the plantar flexors controls the forward progression of the tibia and aligns the GRF vector anterior to the knee joint. The plantar flexors apply their force to the foot that acts as a lever arm to generate a plantar flexion moment around the ankle. Both disrupted plantar flexor function and lever arm deficiency of the foot hinder the plantar flexion – knee extension couple and thus cause crouch gait. Not only the failure of this mechanism, but also the decreased strength of other muscles or other lever arm deficiencies may underlie the observed gait deviations in DS.

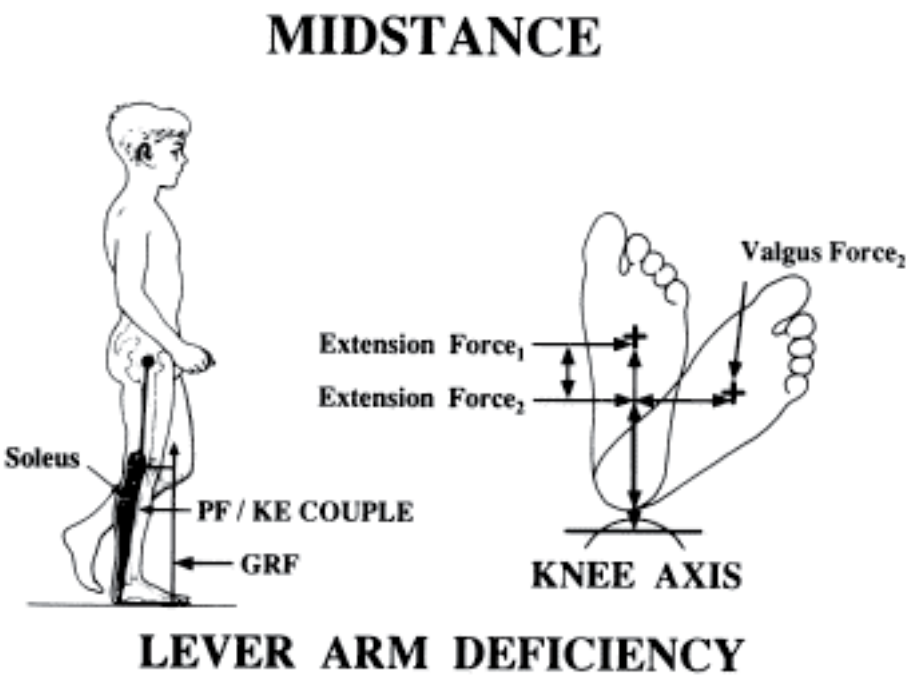


Figure 2. Lever arm deficiency disturbs the plantar flexion - knee-extension (PF / KE) couple. The plantarflexors control the forward displacement of the tibia during midstance and align the ground reaction force (GRF) vector anterior to the knee. The flexible, externally rotated feet shorten the lever arm and consequently reduce the knee extension moment (Gage 1993).

Decreased strength of individual muscles results in increased activation of the weak muscles and compensatory activation of other muscles. Despite mild weakness, normal kinematics may be achieved through compensations, which makes the gait pattern less efficient and thus require more energy, (van der Krogt, Delp, and Schwartz 2012). Especially weakness of the plantar flexors, hip abductors and hip flexors largely affects the efficiency of gait (van der Krogt, Delp, and Schwartz 2012). Crouch gait demands increased knee extensor strength and reduced strength of plantar flexors and hip abductors (Steele et al. 2012). Since measuring strength is challenging in patients with DS, we could not evaluate isolated strength of the aforementioned muscles. Nevertheless, the strength measurements described in chapter 3 pointed towards a generally mild decrease in muscle strength in patients with DS. It remains unclear if this mild weakness alone could cause the observed gait deviations. It is plausible that in combination with lever arm deficiency and impaired motor control, the muscles become 'functionally weak' and fail to generate normal joint moments during gait.

In a normal situation, the lower limb bones act as rigid *lever arms* for optimal application of forces generated by the lower limb muscles and the ground reaction force. Bony malalignment and deformities cause lever arm dysfunction that interferes with the gait pattern. In cerebral palsy, increased femoral anteversion, tibial torsion and foot deformities, as well as muscle

contractions are identified as the main contributors to lever arm dysfunctions (Theologis and Wright 2015; Gage 1993). Rodda et al. (2012) therefore hypothesized that also in patients with DS, abnormal alignment, more specifically increased femoral anteversion, external tibial torsion and pes valgus, contribute to crouch gait with knee flexion contractures as a consequence (Rodda et al. 2012). Indeed, these deviations were observed in patients with DS. However, femoral anteversion seemed only mildly increased and was observed in less than 25% of the patients and contractures were rarely present. Tibial torsion and planovalgus feet on the other hand were more frequently observed. Young children with DS manifest flexible flat feet and large joint mobility. Impaired muscle control might affect the normal development of the foot morphology, which may lead to planus and valgus deformities. The flexible, externally rotated feet shorten the lever arm for the external knee extension moment, which may result in increased knee flexion angles in stance (Figure 2). Secondary to the abnormal load caused by this pathological gait pattern, increased external tibial torsion and planovalgus feet may develop further. However, these deviations were equally present in the 'straight' and 'atypical crouch' group identified by Di Marco. et al (Di Marco et al. 2019) as well as in the three subgroups based on kinetic strategies in chapter 3. This suggests that the observed gait deviations cannot be entirely attributed to lever arm dysfunction but that more factors are involved. Interestingly, in our cohort, we observed patients with severe planovalgus feet and external foot progression that were still able to achieve good knee extension in midstance, as well as patients with normal alignment in stance that did not attain an internal knee extension moment during walking. We hypothesize that lever arm dysfunctions are likely to play a role but are not the only contributing factor to gait deviations in this complex pathological situation.

1.2.3 Motor control hypothesis

Comorbidities in DS are not pure consequences of epileptic seizures, but originate more directly from the genetic mutations (Nabbout et al. 2013), explained by a channelopathy model. Dysfunctional Nav1.1 channels are distributed over the central nervous system and cause neurologic symptoms and developmental deficits, that can be aggravated by status epilepticus (Brunklaus and Zuberi 2014; Catterall 2018). Three theoretical frameworks are presented in literature to link the channelopathy to motor problems: the *cerebellar* role (Kalume et al. 2007), sensorimotor integration deficits (Ricci et al. 2015; Acha et al. 2015) and *motor neuropathy* (Gitiaux et al. 2016)

The *cerebellar* theory is based on mouse models that showed that Nav1.1 channels are largely expressed in the cerebellar Purkinje neurons, where loss-of-function of these channels cause ataxia and related functional deficits (Kalume et al. 2007). Evidence for this mechanism in humans is however lacking (Catterall 2018). Prolonged clumsiness or ataxia-like movements are observed in young children (Scheffer 2012) and cerebellar signs have been reported in adults with DS (Rilstone et al. 2012; Battaglia et al. 2013; Jansen et al. 2006). This led to the hypothesis that disturbed balance and impaired coordination due to cerebellar involvement interferes with gait in patients with DS. This may explain why patients with DS scored lower on functional strength assessments with a large balance and coordination involvement than would be expected from individual muscle strength, as was discussed in chapter 5. A widened base of support and lowered centre of mass (Di Marco et al. 2019) and prolonged support with the CoP under the midfoot (chapter 4) could therefore be interpreted as a strategy to maintain balance. The abnormal kinetic strategies (chapter 3) may partially reflect this impaired muscle coordination.

The *sensorimotor integration* theory proposes that the neural pathways involved in processing sensory information towards motor responses are affected in DS. Evidence supporting this theory showed impaired visuo-motor skills in the early motor development of patients with DS (Chieffo et al. 2011; Ricci et al. 2015) which may be linked to *SCN1A* mutations (Bueichekú et al. 2020). Furthermore, an auditory-motor integration deficit seemed to be involved in speech problems (Chieffo et al. 2016). It has been suggested that this principle could be extended to the integration of vestibular and proprioceptive information, affecting postural stability and gait (Chieffo et al. 2016). According to this theory, crucial pathways in the central motor control of gait and balance (MacKinnon 2018) may be directly affected by the channelopathy in DS, involving sensorimotor integration in addition to cerebellar function.

Impaired sensorimotor integration, especially visual function, was detected in the first stages of psychomotor development and seemed to be responsible for a further delay of cognitive and motor development (Verheyen, Verbecque, et al. 2019; Battaglia et al. 2016; Chieffo et al. 2016). In part I of this discussion, we already stated that gait deviations may reflect cognitive impairments and deficits in psychomotor development. Here, we further elaborate on this hypothesis, proposing that impaired sensorimotor integration may affect the development of gait in young children and may continue to interfere with gait later in life. Based on our own experience during this project, inconsistency of the gait pattern in young participants (<6 years) seemed evident from the large trial-to-trial variability in kinematics and may take longer to resolve than would be expected from normal maturation

(Sutherland 1997; Gouelle et al. 2016). In chapter 3, forward trunk lean was mostly detected in younger patients, while uncompensated crouch gait was more frequently observed in older participants. Young children may rely longer on forward trunk lean, a characteristic of immature gait (Sala and Cohen 2013; Yaguramaki and Kimura 2002), as it helps to generate forward momentum and to align the GRF in front of the knee. With growth, however, this strategy may become insufficient to attain an internal flexion moment at the knee. Patients who then fail to develop an efficient, (close-to-)normal kinetic strategy may evolve towards the uncompensated crouch gait pattern. Longitudinal studies are needed to document the evolution of gait deviations and future research should investigate the possible association between cognition and motor skills.

The *motor neuropathy* theory suggests that the peripheral nervous system is also involved in impaired motor control in patients with DS. Nav1.1 channels are expressed in axons of motor neurons (Duflocq et al. 2008) and channel dysfunction may thus cause innervation problems. Electromyography and nerve conduction studies in patients with DS suggest that motor neuropathy occurs in patients with DS and may be involved in gait deviations (Gitiaux et al. 2016; Dubow, High, and Knupp 2018). But evidence for this theory is limited and obtained in a small number of patients. Further research is needed to support the link between this theory and our findings on gait deviations and muscle function.

2. Methodological considerations

2.1 Study design

Since the aim of this PhD project was to characterize the spontaneous presentation of gait deviations in patients with DS, observational study designs, more specifically cross-sectional studies, were considered the appropriate research design. In part II of this dissertation, three cross-sectional studies were therefore performed. The advantage of this research design is its efficiency in rare diseases and the possibility to collect various outcomes per individual with a relatively short duration. As a disadvantage, selection bias from non-random sampling poses a major risk to the generalisability of the results. Therefore, a consecutive sample of all patients followed-up at department of paediatrics at the University Hospital of Antwerp (UZA) that met the inclusion criteria, was invited to participate in the T-GaiD project. Similarly, participants in the Italian cohort were recruited through neurological departments in three hospitals. Additionally, volunteers were recruited through the parent organization of Flanders

and the Netherlands. The resulting relatively large number of participants enrolled in our project is a strength, especially for a rare disease as DS. We are confident that our sample reflects the total spectrum of children and adolescent with *SCN1A* confirmed DS. A second disadvantage of the cross-sectional study design is its inability to document evolution and causal effects. Comparison of younger with older participants may suggest how gait deviations naturally progress over time, but possible confounders such as improvements in anti-epileptic medication, physiotherapeutic and orthopaedic interventions should be taken into account. Furthermore, we did not aim to establish a classification system of gait deviations and did not perform data collection and analyses that would be suitable for such an objective. Classification of gait patterns is only relevant when it can guide the management of gait deviations. Hereto, possible prognostic factors should be detected and appropriate statistical methods are needed to identify clusters of gait deviation linked to specific clinical factors (Rozumalski and Schwartz 2009). It remains unclear whether the observed subgroups based on kinetic strategies (chapter 3) or foot strike pattern (chapter 4) can be considered as separate patterns due to a distinct causal mechanism, or as different ends of the same spectrum on which natural evolution may evolve from one pattern to another. For thorough understanding of the development of gait deviations in patients with DS, longitudinal studies are needed.

2.2 Data collection

The central data collection method in this project was 3DGA, following the protocol described in detail in chapters 1 and 3. Since the T-GaiD project established its protocol before the start in 2017 and longitudinal follow-up was required, major changes were undesirable. However, experience and new insights during data collection have revealed drawbacks and potential improvements to the protocol that will be discussed in the next paragraphs.

In chapter 3, kinetic strategies were distinguished based on knee extension moment and trunk lean. The inclination of the trunk was estimated based on video images, instead of 3D registration using a marker set that included a trunk segment (Davis et al. 1991; Heyrman et al. 2013). This estimation was less objective and prone to errors due to projection errors or reduced visibility. The lower body model was adopted in our protocol, as the project focussed on lower limb joint kinematics and kinetics. Furthermore, this choice was made to reduce the duration and burden of the gait analysis session by using the minimum amount of markers. Our own experience also showed that many participants did not like to take off their shirt, which triggered difficult behaviour. However, since a reliable estimation is

necessary for thorough interpretation of lower limb kinetics, we recommend to use a trunk segment for future instrumented 3DGA in patients with DS.

Reducing the preparation time and discomfort when removing markers seemed to improve the collaboration of participants. For this reason, EMG, which was part of the original protocol, could only be performed when good cooperation of the participants was assured. Thus far, EMG signals were only interpreted qualitatively for individual participants, as part of the clinical interpretation of the gait analysis data. But an EMG dataset of a limited number of patients is available for future research. Although it is challenging to acquire good quality EMG data in this population, future investigation of muscle activation patterns is needed and worth the try. In clinical practice, EMG may be optional for good cooperative patients or required for specific clinical questions.

Collecting good quality 3DGA data remains challenging in this population. It is essential that participants walk in a representative manner for their usual gait. Due to cognitive and behavioural impairments, various patients, especially young children or those with profound ID, had to perform a large amount of trials before a reasonable number of useful steps was collected. They tended to run, walk in a playful manner or did not follow a straight line. Furthermore, when participants pull the markers off, 3D data cannot be collected. For those patients, 2D video analysis may offer a suitable alternative, although we recommend the use of instrumented 3DGA, as it provides insight into muscle work and motor control that can only be obtained by kinematic and kinetic analyses. Moderate to good validity and reliability (unpublished findings (Verheyen, Wyers, et al. 2019; Cornelissen and De Swert 2019)) was found for the use of two observational scales in patients with DS: the Edinburgh Visual Gait Score (Read et al. 2003) and the Observational Gait Scale (Rancho Los Amigos National Rehabilitation Center 2001). The use of a validated scale improves the objectivity and reproducibility of video gait assessment. Pedobarography can be performed in addition to a video gait assessment without a need for markers, in order to obtain quantitative information on dynamic foot function. In chapter 4, we suggested that this approach may offer insight into motor control during gait. In the near future, the use of markers may even become obsolete in 3DGA, as promising advances are being made in the development of markerless motion capture techniques (Sandau et al. 2014; Ceseracciu, Sawacha, and Cobelli 2014).

Instrumented gait analysis usually includes standardized physical examination to enable clinical interpretation of the results (Baker et al. 2016). As discussed in chapter 5, good quality gait analysis data are prioritized, leaving limited time and possibly reduced patient cooperation for the physical examination. Strength measurements were even more challenging in this

context. We compared different methods to assess muscle strength and concluded that HHD may be preferred as a sensitive, quantitative estimate of individual muscle strength. A ceiling effect was detected when using MMT and these scores may not be sensitive enough to document change over time (Bohannon 2005). Items of the FSM were difficult for our participants to perform correctly: they could not jump with two feet simultaneously, wanted to throw the bean bag sideways or even overarm, did not understand the meaning of 'as much/far as possible', etc. In the context of gait analysis, the FSM may not be adequate to document muscle strength. In other clinical contexts however, practitioners may be interested in functional muscle strength as an outcome, for example related to functional strength training during physical education or physiotherapy sessions. In case the test items can be practiced, the FSM may be more feasible than during gait analysis. However, we hypothesize that construct validity in this population may be lower than the established values in children with a TD (Aertssen, Ferguson, and Smits-Engelsman 2016) or general ID (Aertssen, Steenbergen, and Smits-Engelsman 2018), owing to balance and cognitive impairments as discussed under 'motor control hypothesis'.

3. Clinical implications

3.1 Evaluation

There is strong consensus that screening for gait disorders should be routinely performed in the follow-up of patients with DS (Wirrell et al. 2017) and instrumented gait analysis should be considered (Vereniging Klinische Genetica Nederland 2019). Part I and part II both illustrated the importance of objective, quantitative analysis of 3D kinematics and kinetics. As discussed before, in young children and patients with profound ID, 2D video analysis may be a valid alternative approach. And even for good cooperative patients, this method may provide sufficient information for routine screening. However, for the early detection of gait deviations or deterioration over time, for thorough understanding of the occurrence of deviations in an individual patient and to guide individually tailored interventions, instrumented 3DGA is needed. We therefore recommend to perform 3DGA at critical time points in the follow-up of patients with DS, supplemented with video analysis in between 3DGA sessions. In addition to this scheme, 3DGA should be performed when worrisome clinical observations such as quick deterioration are made, or if an orthopaedic or surgical intervention is being considered.

Physical examination is required as part of gait analysis to detect musculoskeletal abnormalities that may be cause or consequence of the pathological gait pattern. More specifically, foot deformities and rotational deformities of the long bones in the lower limb should be evaluated to document lever arm dysfunction. Strength assessments are desirable, if possible. Furthermore, muscle shortening, joint contractures and patella alta are associated with crouch gait in cerebral palsy (Rodda et al. 2004; Armand, Decoulon, and Bonnefoy-Mazure 2016) and should therefore also be evaluated in patients with DS. Radiography is usually not part of standard evaluation, but might be indicated in individual patients with disturbing bony deformities.

Not only insight into the mechanics of gait is needed to guide the selection of appropriate interventions. Since cognitive and motor development seemed to be largely involved (see 'motor control hypothesis'), structured evaluation using developmental scales, gross motor function measures or balance tests are desired in addition to gait analysis. Future studies should document which tests are feasible and valid in this population.

3.2 Treatment

Based on gait analysis results, individually tailored interventions can be planned to prevent deterioration of the gait pattern or to improve existing walking problems. Hereto, a clinical report containing gait analysis results including comparison with previous sessions should be prepared and discussed with the treating neuropediatric physician. The results could also be shared with other professionals in the multidisciplinary team, such as physiotherapists, physiatrists or orthopaedic surgeons. Indications for interventions are related to the musculoskeletal and motor control hypotheses previously discussed. Lever arm dysfunction may be targeted using orthotics or exceptionally surgery (Theologis 2013). Decreased muscle strength may form an indication for strength training (Damiano and Dodd 2002). Early stimulation of motor development in young children and gait training to stimulate the development of adequate kinetic strategies when growing up, might make an important difference in the prevention of walking problems at a later age. Altogether, an integrated approach to the complex aspects contributing to walking problems is needed, with the aim of prevention and treatment of gait deviations. However, evidence for the effectiveness of such interventions has not yet been established in this population. During the T-GaiD project, multidisciplinary meetings with neuropediatricians, physiotherapists and gait analysis experts were organised to discuss 3DGA and physical examination findings of individual patients. Individual advice was formulated, treatment plans were adjusted and referral to

specialists were made. In the next paragraphs, the clinical experience gained throughout this project will therefore be discussed.

Restoration of lever arm function is often a goal of surgical interventions for crouch gait in patients with cerebral palsy, including tibial derotation or planovalgus correction (Novacheck and Gage 2007; Kadhim and Miller 2014; Theologis 2013). In patients with DS however, surgery is rarely indicated for various reasons. First, the individual contribution of bony deformities in the causal complex of gait deviations is not yet sufficiently understood. Second, the effectiveness of surgical interventions largely depends on post-operative rehabilitation, which is complicated by cognition and behaviour characteristics in DS. Furthermore, adverse effects should be avoided in this complex pathology. Insoles or orthopaedic shoes are frequently prescribed to support the foot arch and prevent worsening deformities and pain. In combination with a good shoe, extra stability around the foot and ankle might slightly improve the lever arm function of the foot. Literature suggests that ankle foot orthoses (AFO) (Buckon et al. 2004) or more specifically floor reaction orthoses (Böhm et al. 2018; Rogozinski et al. 2009) can effectively improve crouch gait in patients with cerebral palsy. These devices restrict the ankle dorsiflexion motion during the stance phase, which helps to restore the plantar flexion – knee extension couple and reduce the external flexion moment around the knee. In our cohort, three younger children received rigid AFO's in the course of the project. They had severe intellectual disabilities and their barefoot pattern was characterized by forward trunk lean and increased knee flexion. With AFO's, the gait pattern generally improved compared to barefoot, but ankle range of motion and push-off power were limited, which is a known disadvantage of any AFO that limits ankle motion. Two children only used their orthoses for a limited number of hours per week at school. This approach aimed to prevent further evolution towards inefficient kinetic strategies and progressive crouch gait by providing stability and external correction of the plantar flexion – knee extension couple when wearing the orthosis. The aim was not to introduce the AFO as a permanent walking aid. The rationale was that walking barefoot and with normal shoes was needed to maintain and improve plantar flexor function. Evaluation of the gait pattern after one year of AFO use in these participants indicated that even the barefoot pattern improved, suggesting that the motor development may have benefited from this approach. Future studies are needed to document the indications and effectiveness of orthotics in this population.

Most participants received physiotherapy at their school for special education or day care facility. It was assumed that those sessions aimed to support school activities by focussing on fine motor skills and psychomotor development in addition to gross motor skills.

Physiotherapy sessions in private practice have increasingly been prescribed to specifically target walking problems. An inventory of the physiotherapeutic interventions that our participants received, is currently being established.

4. Future research

This PhD project was part of a larger research project "T-GaiD" at the University of Antwerp, the Antwerp University Hospital and the KU Leuven and performed in collaboration with an ongoing study at the University Hospital of Padova. Both research projects performed longitudinal follow-up assessments of children, adolescents and young adults with DS using 3DGA. These longitudinal studies are needed to document the evolution of gait over time, to detect prognostic factors and to identify the intervals or critical time points at which 3DGA should be performed. For this dissertation, analyses were limited to the sagittal plane. However, future analyses of the other planes and cross-plane interaction should provide further insight into the pathological processes. The continuation of 3DGA in clinical follow-up of patients with DS will result in a gait analysis dataset enabling studies on the association between clinical or genetic factors and gait that require larger sample sizes. At present, national and international collaborations are creating registers that combine genetic and clinical datasets (e.g. www.platform-residras.com). Adopting uniform, standardized gait data into international registers will enable large scale analysis of walking problems in DS. Furthermore, objective and quantitative measures of gait derived from 3DGA, could be used as outcome parameters in other research domains, for example in pharmacology or genetics. Gait indices such as the Gait Deviation Index (M. H. Schwartz and Rozumalski 2008) or Gait Profile Score (Baker et al. 2009) may be suitable for this purpose. Their validity and sensitivity in patients with DS are currently under investigation in the T-GaiD project. As mentioned before, EMG could be performed as part of 3DGA to investigate the muscle activation pattern to establish the link between biomechanical observations and neuromotor control. Although collecting good quality EMG data was challenging in this population, we already obtained a first dataset from a small number of our participants.

Besides gait analysis, further insight into the pathophysiology behind gait deviations is needed. Knowledge on genetics of DS and pharmacological management of epilepsy in DS is rapidly improving, which leads to increased awareness, more accurate diagnosis and significantly improved seizure management (Samanta 2020; Ziobro et al. 2018). Younger children may have a better prognosis of comorbidities including gait, as secondary

deterioration owing to epileptic seizures may be reduced compared to previous generations. In a far future, gene therapy may even become able to restore the sodium channel function and eliminate epilepsy in certain patients with DS, but this research is still in an very early stage. Future investigations of the link between genetics, epilepsy and gait are needed for thorough understanding and further improved management of walking problems in patients with DS.

Bibliography

Bibliography

Abbruzzese, L. D. et al. (2016) 'Temporal and spatial gait parameters in children with Cri du Chat Syndrome under single and dual task conditions', Gait Posture. 2016/10/25. Elsevier B.V., 50, pp. 47–52. doi: 10.1016/j.gaitpost.2016.08.006.

Acha, J. et al. (2015) 'Cognitive characterization of children with Dravet syndrome: A neurodevelopmental perspective', Child Neuropsychology. Routledge, 21(5), pp. 693–715. doi: 10.1080/09297049.2014.959480.

Aertssen, W. F. M. et al. (2019) 'Functional strength measurement in cerebral palsy: feasibility, test–retest reliability, and construct validity', Developmental Neurorehabilitation. Taylor & Francis, 22(7), pp. 453–461. doi: 10.1080/17518423.2018.1518963.

Aertssen, W. F. M., Ferguson, G. D. and Smits-Engelsman, B. C. M. (2016) 'Reliability and Structural and Construct Validity of the Functional Strength Measurement in Children Aged 4 to 10 Years', Physical Therapy, 96(6), pp. 888–897. doi: 10.2522/ptj.20140018.

Aertssen, W. F. M. and Smits-Engelsman, B. C. M. (2012) 'Functional Strength Measurement (FSM): Manual.' Meteren, the Netherlands: FSM Production.

Aertssen, W. F. M., Steenbergen, B. and Smits-Engelsman, B. C. M. (2018) 'The validity and reliability of the Functional Strength Measurement (FSM) in children with intellectual disabilities', Journal of Intellectual Disability Research, 62(8), pp. 719–729. doi: 10.1111/jir.12508.

Aitkens, S. et al. (1989) 'Relationship of manual muscle testing to objective strength measurements', Muscle and Nerve, 12(3), pp. 173–177. doi: https://doi.org/10.1002/mus.880120302.

Aljaafari, D. et al. (2017) 'Adult motor phenotype differentiates Dravet syndrome from Lennox-Gastaut syndrome and links SCN1A to early onset parkinsonian features', Epilepsia, 58(3), pp. e44–e48. doi: 10.1111/epi.13692.

Almuhtaseb, S., Oppewal, A. and Hilgenkamp, T. I. M. (2014) 'Gait characteristics in individuals with intellectual disabilities: A literature review', Research in Developmental Disabilities. 2014/08/12. Elsevier Ltd., 35(11), pp. 2858–2883. doi: 10.1016/j.ridd.2014.07.017.

Ambrose, A. F., Paul, G. and Hausdorff, J. M. (2013) 'Risk factors for falls among older adults: a review of the literature', Maturitas, 75(1), pp. 51–61. doi: 10.1016/j.maturitas.2013.02.009.

Armand, S., Decoulon, G. and Bonnefoy-Mazure, A. (2016) 'Gait analysis in children with cerebral palsy', EFORT Open Reviews, 1(12), pp. 448–460. doi: 10.1302/2058-5241.1.000052.

Baker, R. W. (2006) 'Gait analysis methods in rehabilitation', Journal of NeuroEngineering and Rehabilitation, 3, pp. 1–10. doi: 10.1186/1743-0003-3-4.

Baker, R. W. et al. (2009) 'The Gait Profile Score and Movement Analysis Profile', Gait and Posture, 30(3), pp. 265–269. doi: 10.1016/j.gaitpost.2009.05.020.

Baker, R. W. et al. (2012) 'The minimal clinically important difference for the Gait Profile Score', Gait and Posture. Elsevier B.V., 35(4), pp. 612–615. doi: 10.1016/j.gaitpost.2011.12.008.

Baker, R. W. (2013) Measuring walking: a handbook of clinical gait analysis. Mac Keith Press.

Baker, R. W. et al. (2016) 'Gait analysis: Clinical facts', European Journal of Physical and Rehabilitation Medicine, 52(4), pp. 560–574.

Balasubramanian, S. et al. (2015) 'On the analysis of movement smoothness', Journal of NeuroEngineering and Rehabilitation. Journal of NeuroEngineering and Rehabilitation, 12(1), pp. 1–11. doi: 10.1186/s12984-015-0090-9.

Bates, D. et al. (2015) 'Fitting linear mixed-effects models using lme4', Journal of Statistical Software, 67(1). doi: 10.18637/jss.v067.i01.

Battaglia, D. et al. (2013) 'Cognitive decline in Dravet syndrome: Is there a cerebellar role?', Epilepsy Research. Elsevier B.V., 106(1–2), pp. 211–221. doi: 10.1016/j.eplepsyres.2013.03.012.

Battaglia, D. et al. (2016) 'Outlining a core neuropsychological phenotype for Dravet syndrome', Epilepsy Research. Elsevier B.V., 120, pp. 91–97. doi: 10.1016/j.eplepsyres.2015.11.020.

Beasly, W. C. and Beasley, W. C. (1956) 'Influence of method on estimates of normal knee extensor force among normal and postpolio children', Phys Ther Rev. 1956/01/01. United States, 36(1), pp. 21–41. doi: 10.1093/ptj/36.1.21.

Beenakker, E. A. C. et al. (2001) 'Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry', Neuromuscular Disorders, 11(5), pp. 441–446. doi: 10.1016/S0960-8966(01)00193-6.

van den Beld, W. A. et al. (2006a) 'Validity and reproducibility of hand-held dynamometry in children aged 4-11 years', Journal of Rehabilitation Medicine, 38(1), pp. 57–64. doi: 10.1080/16501970510044043.

van den Beld, W. A. et al. (2006b) 'Validity and reproducibility of the jamar dynamometer in children aged 4-11 years', Disability and Rehabilitation, 28(21), pp. 1303–1309. doi: 10.1080/09638280600631047.

van den Beld, W. A. et al. (2011) 'Comparison of 3 instruments to measure muscle strength in children: A prospective study', European Journal of Paediatric Neurology, 15(6), pp. 512–518. doi: 10.1016/j.ejpn.2011.05.006.

Benjamini, Y. and Hochberg, Y. (1995) 'Controlling the False Discovery Rate : A Practical and Powerful Approach to Multiple Testing', 57(1), pp. 289–300. Available at: https://www.jstor.org/stable/2346101.

Bertsch, C. et al. (2004) 'Evaluation of early walking patterns from plantar pressure distribution measurements. First year results of 42 children', Gait and Posture, 19(3), pp. 235–242. doi: 10.1016/S0966-6362(03)00064-X.

Bevans, J. S. (1992) 'Biomechanics: a review of foot function in gait', The Foot, 2(2), pp. 79–82. doi: 10.1016/0958-2592(92)90022-H.

Bishop, S. L. et al. (2016) 'Autism Spectrum Disorder, Intellectual Disability, and Delayed Walking', Pediatrics. 2016/02/26, 137(3), p. e20152959. doi: 10.1542/peds.2015-2959.

Bohannon, R. W. (1988) 'Make Tests and Break Tests of Elbow Flexor Muscle Strength', Physical Therapy, 68(2), pp. 193–194. doi: 10.1093/ptj/68.2.193.

Bohannon, R. W. (2005) 'Manual muscle testing: Does it meet the standards of an adequate screening test?', Clinical Rehabilitation, 19(6), pp. 662–667. doi: 10.1191/0269215505cr873oa.

Bohannon, R. W. (2019) 'Considerations and practical options for measuring muscle strength: A narrative review', BioMed Research International. Hindawi, 2019. doi: 10.1155/2019/8194537.

Bohannon, R. W., Wang, Y.-C. and Noonan, C. (2019) 'Relationships between grip strength, dexterity, and fine hand use are attenuated by age in children 3 to 13 years-of-age', Journal of Physical Therapy Science, 31(4), pp. 382–386. doi: 10.1589/jpts.31.382.

Böhm, H. et al. (2018) 'Effect of floor reaction ankle–foot orthosis on crouch gait in patients with cerebral palsy: What can be expected?', Prosthetics and Orthotics International, 42(3), pp. 245–253. doi: 10.1177/0309364617716240.

Brown, A. et al. (2020) 'Cognitive, behavioral, and social functioning in children and adults with Dravet syndrome', Epilepsy and Behavior. Elsevier Inc., 112, p. 107319. doi: 10.1016/j.yebeh.2020.107319.

Brunklaus, A. et al. (2012) 'Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome', Brain, 135(8), pp. 2329–2336. doi: 10.1093/brain/aws151.

Brunklaus, A. and Zuberi, S. M. (2014) 'Dravet syndrome - From epileptic encephalopathy to channelopathy', Epilepsia, 55(7), pp. 979–984. doi: 10.1111/epi.12652.

Brunner, R. and Rutz, E. (2013) 'Biomechanics and muscle function during gait', Journal of Children's Orthopaedics, 7(5), pp. 367–371. doi: 10.1007/s11832-013-0508-5.

Buckon, C. E. et al. (2004) 'Comparison of three ankle-foot orthosis configurations for children with spastic diplegia', Developmental Medicine and Child Neurology, 46(9), pp. 590–598. doi: 10.1017/S0012162204001008.

Bueichekú, E. et al. (2020) 'Central neurogenetic signatures of the visuomotor integration system', Proceedings of the National Academy of Sciences of the United States of America, 117(12), pp. 6836–6843. doi: 10.1073/pnas.1912429117.

Callisaya, M. L. et al. (2010) 'Ageing and gait variability--a population-based study of older people', Age Ageing. 2010/01/20, 39(2), pp. 191–197. doi: 10.1093/ageing/afp250.

Camfield, P., Camfield, C. and Nolan, K. (2016) 'Helping Families Cope with the Severe Stress of Dravet Syndrome', Canadian Journal of Neurological Sciences. 2016/06/07, 43(S3), pp. S9–S12. doi: 10.1017/cjn.2016.248.

Catterall, W. A. (2018) 'Dravet syndrome: a sodium channel interneuronopathy', Current Opinion in Physiology. Elsevier Ltd, 2, pp. 42–50. doi: 10.1016/j.cophys.2017.12.007.

Cazalets, J. R. et al. (2017) 'Evaluation of Motor Skills in Children with Rubinstein–Taybi Syndrome', Journal of Autism and Developmental Disorders. Springer US, 47(11), pp. 3321–3332. doi: 10.1007/s10803-017-3259-1.

Ceseracciu, E., Sawacha, Z. and Cobelli, C. (2014) 'Comparison of markerless and marker-based motion capture technologies through simultaneous data collection during gait: Proof of concept', PLoS ONE, 9(3), pp. 1–7. doi: 10.1371/journal.pone.0087640.

Ceulemans, B. (2011) 'Overall management of patients with Dravet syndrome', Developmental Medicine and Child Neurology, 53(SUPPL. 2), pp. 19–23. doi: 10.1111/j.1469-8749.2011.03968.x.

Ceulemans, B. and Cras, P. (2004) '"Severe myoclonic epilepsy in infancy" relevance for the clinician of severe epilepsy starting in infancy', Acta Neurologica Belgica, 104(3), pp. 95–99.

Chieffo, D. et al. (2011) 'Early development in Dravet syndrome; visual function impairment precedes cognitive decline', Epilepsy Research. Elsevier B.V., 93(1), pp. 73–79. doi: 10.1016/j.eplepsyres.2010.10.015.

Chieffo, D. et al. (2016) 'Disorders of early language development in Dravet syndrome', Epilepsy and Behavior. Elsevier Inc., 54, pp. 30–33. doi: 10.1016/j.yebeh.2015.10.027.

Cimolin, V. et al. (2014) 'Gait strategy in genetically obese patients: a 7-year follow up', Res Dev Disabil. 2014/04/26. Elsevier Ltd., 35(7), pp. 1501–1506. doi: 10.1016/j.ridd.2014.04.005.

Claes, L. et al. (2001) 'De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy', American Journal of Human Genetics. doi: 10.1086/320609.

De Cock, A. et al. (2008) 'The trajectory of the centre of pressure during barefoot running as a potential measure for foot function', Gait & Posture, 27(4), pp. 669–675. doi: 10.1016/j.gaitpost.2007.08.013.

Cornelissen, K. and De Swert, S. (2019) Validity and inter-rater reliability of 2D video gait analysis in children with Dravet Syndrome. Universiteit Antwerpen.

Cross, J. H. et al. (2019) 'Dravet syndrome: Treatment options and management of prolonged seizures', Epilepsia, 60(S3), pp. S39–S48. doi: 10.1111/epi.16334.

Damiano, D. L. and Dodd, K. (2002) 'Should we be testing and training muscle strength in cerebral palsy?', Developmental Medicine and Child Neurology, 44(1), pp. 68–72. doi: 10.1111/j.1469-8749.2002.tb00262.x.

Darra, F. et al. (2019) 'Dravet syndrome: Early electroclinical findings and long-term outcome in adolescents and adults', Epilepsia, 60(S3), pp. S49–S58. doi: 10.1111/epi.16297.

Davids, J. R. and Bagley, A. M. (2014) 'Identification of common gait disruption patterns in children with cerebral palsy', Journal of the American Academy of Orthopaedic Surgeons, 22(12), pp. 782–790. doi: 10.5435/JAAOS-22-12-782.

Davids, J. R., Gibson, T. W. and Pugh, L. I. (2005) 'Quantitative Segmental Analysis of Weight-Bearing Radiographs of the Foot and Ankle for Children, Normal Alignment', J pediatr Orthop, 25(6), pp. 769–776.

Davis, R. B. et al. (1991) 'A gait analysis data collection and reduction technique', Human Movement Science, 10, pp. 575–597.

Depienne, C. et al. (2009) 'Spectrum of SCN1A gene mutations associated with Dravet syndrome: Analysis of 333 patients', Journal of Medical Genetics, 46(3), pp. 183–191. doi: 10.1136/jmg.2008.062323.

Deschamps, K. et al. (2011) 'Body of evidence supporting the clinical use of 3D multisegment foot models: A systematic review', Gait and Posture. Elsevier B.V., 33(3), pp. 338–349. doi: 10.1016/j.gaitpost.2010.12.018.

Deschamps, K. et al. (2015) 'Review of clinical approaches and diagnostic quantities used in pedobarograpic measurements', J Sports Med Phys Fitness, 55, pp. 191–204.

Desloovere, K. et al. (2006) 'Do dynamic and static clinical measurements correlate with gait analysis parameters in children with cerebral palsy?', Gait and Posture, 24(3), pp. 302–313. doi: 10.1016/j.gaitpost.2005.10.008.

Djukic, A. et al. (2016) 'Pharmacologic Treatment of Rett Syndrome With Glatiramer Acetate', Pediatr Neurol. 2016/07/02. Elsevier Inc, 61, pp. 51–57. doi: 10.1016/j.pediatrneurol.2016.05.010.

Dockstader, C. et al. (2012) 'White matter maturation in visual and motor areas predicts the latency of visual activation in children', Hum Brain Mapp. 2011/03/25, 33(1), pp. 179–191. doi: 10.1002/hbm.21203.

Douma, R. K. W. et al. (2014) 'Reference values for isometric muscle force among workers for the Netherlands: a comparison of reference values', BMC Sports Science, Medicine and Rehabilitation, 6(1), p. 10. doi: 10.1186/2052-1847-6-10.

Dravet, C. (1978) 'Les épilepsies graves de l'enfant', Vie Med, 8, pp. 543–548.

Dravet, C. (2011) 'The core Dravet syndrome phenotype', Epilepsia, 52(SUPPL. 2), pp. 3–9. doi: 10.1111/j.1528-1167.2011.02994.x.

Dubow, E., High, B.-A. and Knupp, K. G. (2018) Electromyography and Nerve Conduction Studies (EMG/NCS) in Dravet Syndrome, American Epilepsy Society (AES) Annual Meeting Abstracts. Available at: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/502525 (Accessed: 10 November 2020).

Duflocq, A. et al. (2008) 'Nav1.1 is predominantly expressed in nodes of Ranvier and axon initial segments', Molecular and Cellular Neuroscience, 39(2), pp. 180–192. doi: 10.1016/j.mcn.2008.06.008.

Escolar, D. M. et al. (2001) 'Clinical evaluator reliability for quantitative and manual muscle testing measures of strength in children', Muscle and Nerve, 24(6), pp. 787–793. doi: 10.1002/mus.1070.

Fasano, A. et al. (2014) 'Antecollis and levodopa-responsive parkinsonism are late features of Dravet syndrome', Neurology. 2014/05/23, 82(24), pp. 2250–2251. doi: 10.1212/wnl.0000000000000521.

Franki, I. et al. (2015) 'An evaluator-blinded randomized controlled trial evaluating therapy effects and prognostic factors for a general and an individually defined physical therapy program in ambulant children with bilateral spastic cerebral palsy', Eur J Phys Rehabil Med, 51, pp. 677–691.

Fuller, E. A. (1999) 'Center of pressure and its theoretical relationship to foot pathology.', Journal of the American Podiatric Medical Association, 89(6), pp. 278–291. doi: 10.7547/87507315-89-6-278.

Gage, James R. (1993) 'Gait Analysis; an essential tool in the treatment of Cerebral Palsy', Clinical Orthopaedics and Related Research, 288, pp. 126–134.

Gage, J R (1993) 'Gait analysis in cerebral palsy treatment', Clinical Orthopaedics and Related Research, 288, pp. 126–134.

Gage, J. R., Deluca, P. and Renshaw, T. (1995) 'Gait analysis: principles and applications', J.Bone Joint Surg., 77-A(10), pp. 1607–1623. Available at: Ann Hallemans.

Gallahue, D. L. and Ozmun, J. C. (1998) 'Fundamental Movement Abilities', in Understanding Motor Development: Infants, Children, Adolescents, Adults. 4th edn. Boston, Massachusetts: McGraw-Hill, p. 541.

Galli, M., Cimolin, V., Pau, M., et al. (2014) 'Relationship between flat foot condition and gait pattern alterations in children with Down syndrome', J Intellect Disabil Res. 2013/01/08, 58(3), pp. 269–276. doi: 10.1111/jir.12007.

Galli, M., Cimolin, V., Rigoldi, C., et al. (2014) 'The effects of low arched feet on foot rotation during gait in children with down syndrome', Journal of Intellectual Disability Research. 2014/04/23, 58(8), pp. 758–764. doi: 10.1111/jir.12087.

Galli, M. et al. (2015) 'Effects of obesity on gait pattern in young individuals with Down syndrome', Int J Rehabil Res. 2014/11/25, 38(1), pp. 55–60. doi: 10.1097/mrr.0000000000000092.

Giacomozzi, C. and Stebbins, J. A. (2017) 'Anatomical masking of pressure footprints based on the Oxford Foot Model: validation and clinical relevance', Gait and Posture. Elsevier B.V., 53, pp. 131–138. doi: 10.1016/j.gaitpost.2016.12.022.

Gillespie, M. (2003) 'Cardiovascular Fitness of Young Canadian Children with and without Mental Retardation Author (s): Mike Gillespie Source : Education and Training in Developmental Disabilities , September 2003 , Vol . 38 , Published by : Division on Autism and Developmen', 38(3), pp. 296–301.

Gitiaux, C. et al. (2016) 'Motor neuropathy contributes to crouching in patients with Dravet syndrome', Neurology, 87(3), pp. 277–281. doi: 10.1212/WNL.0000000000002859.

Gouelle, A. et al. (2016) 'Changes in Gait Variability From First Steps to Adulthood: Normative Data for the Gait Variability Index', Journal of Motor Behavior, 48(3), pp. 249–255. doi: 10.1080/00222895.2015.1084986.

Graham, K. et al. (2004) 'The Functional Mobility Scale (FMS)', Journal of Pediatric Orthopaedics, 24(5), pp. 514–520. doi: 10.1097/01241398-200409000-00011.

Greenspan, S. and Woods, G. W. (2014) 'Intellectual disability as a disorder of reasoning and judgement: The gradual move away from intelligence quotient-ceilings', Current Opinion in Psychiatry, 27(2), pp. 110–116. doi: 10.1097/YCO.0000000000000037.

Grunt, S. et al. (no date) 'Reproducibility of video screen measurements of sagittal joint angles during gait in patients with spastic cerebral palsy', in JEGM 2010.

Hallemans, A. et al. (2005) '3D joint dynamics of walking in toddlers - A cross-sectional study spanning the first rapid development phase of walking', Gait & Posture, 22(2), pp. 107–118. doi: 10.1016/j.gaitpost.2004.07.010.

Hallemans, A. et al. (2006) 'Changes in foot-function parameters during the first 5 months after the onset of independent walking: A longitudinal follow-up study', Gait and Posture, 23(2), pp. 142–148. doi: 10.1016/j.gaitpost.2005.01.003.

Hallemans, A. et al. (2016) 'Gait impairment in Dravet syndrome: First results from a pilot study', Gait & Posture. Elsevier B.V., 49, pp. 186–187. doi: 10.1016/j.gaitpost.2016.07.241.

Hallemans, A. et al. (2019) 'Clinical usefulness and challenges of instrumented motion analysis in patients with intellectual disabilities', Gait and Posture, 71, pp. 105–115. doi: 10.1016/j.gaitpost.2019.04.016.

Hallemans, A., De Clercq, D. and Aerts, P. (2006) 'Changes in 3D joint dynamics during the first 5 months after the onset of independent walking: A longitudinal follow-up study', Gait & Posture, 24(3), pp. 270–279. doi: 10.1016/j.gaitpost.2005.10.003.

Hartman, E. et al. (2010) 'On the relationship between motor performance and executive functioning in children with intellectual disabilities', J Intellect Disabil Res. 2010/06/12, 54(5), pp. 468–477. doi: 10.1111/j.1365-2788.2010.01284.x.

Herzog, R. et al. (2013) 'Are healthcare workers intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review', BMC Public Health, 13(1). doi: 10.1186/1471-2458-13-154.

Heyrman, L. et al. (2013) 'Reliability of head and trunk kinematics during gait in children with spastic diplegia', Gait and Posture, 37(3), pp. 424–429. doi: 10.1016/j.gaitpost.2012.08.021.

Heyrman, L. et al. (2014) 'Altered trunk movements during gait in children with spastic diplegia: Compensatory or underlying trunk control deficit?', Research in Developmental Disabilities. Elsevier Ltd., 35(9), pp. 2044–2052. doi: 10.1016/j.ridd.2014.04.031.

Hislop, H. J. and Montgomery, J. (2007) Daniels and Worthingham's Muscle Testing: Techniques of Manual Examination. 8th edn, Elsevier Inc. 8th edn. WB Saunders Co.

Hoang, H. X. and Reinbolt, J. A. (2012) 'Crouched posture maximizes ground reaction forces generated by muscles', Gait and Posture. Elsevier B.V., 36(3), pp. 405–408. doi: 10.1016/j.gaitpost.2012.03.020.

Hocking, D. R. et al. (2014) 'Gait profiles as indicators of domain-specific impairments in executive control across neurodevelopmental disorders', Res Dev Disabil. 2013/11/02. Elsevier Ltd, 35(1), pp. 203–214.

doi: 10.1016/j.ridd.2013.10.005.

Hof, A. L. (1996) 'Scaling gait data to body size', Gait and Posture, 4(3), pp. 222–223. doi: 10.1016/0966-6362(95)01057-2.

Hof, A. L. (2000) 'On the Interpretation of the Support Moment', Gait and Posture, 12, pp. 196–199. doi: 10.1016/S0966-6362(00)00084-9.

Horvat, M. et al. (2013) 'The influence of dual-task conditions on movement in young adults with and without Down syndrome', Res Dev Disabil. 2013/08/22. Elsevier Ltd, 34(10), pp. 3517–3525. doi: 10.1016/j.ridd.2013.06.038.

Horvat, M., Pitetti, K. H. and Croce, R. (1997) 'Isokinetic torque, average power, and flexion/extension ratios in nondisabled adults and adults with mental retardation', Journal of Orthopaedic and Sports Physical Therapy, 25(6), pp. 395–399. doi: 10.2519/jospt.1997.25.6.395.

Houwen, S. et al. (2016) 'The interrelationships between motor, cognitive, and language development in children with and without intellectual and developmental disabilities', Res Dev Disabil. 2016/02/07, 53–54, pp. 19–31. doi: 10.1016/j.ridd.2016.01.012.

Iosa, M. et al. (2014) 'Assessment of upper body accelerations in young adults with intellectual disabilities while walking, running, and dual-task running', Hum Mov Sci. 2014/03/19. Elsevier B.V., 34(1), pp. 187–195. doi: 10.1016/j.humov.2014.02.005.

Jameson, E. G. et al. (2008) 'Dynamic pedobarography for children: Use of the center of pressure progression', Journal of Pediatric Orthopaedics, 28(2), pp. 254–258. doi: 10.1097/BPO.0b013e318164ee6e.

Jansen, F. E. et al. (2006) 'Severe myoclonic epilepsy of infancy (Dravet syndrome): Recognition and diagnosis in adults', Neurology, 67(12), pp. 2224–2226. doi: 10.1212/01.wnl.0000249312.73155.7d.

Kadhim, M. and Miller, F. (2014) 'Crouch gait changes after planovalgus foot deformity correction in ambulatory children with cerebral palsy', Gait and Posture. Elsevier B.V., 39(2), pp. 793–798. doi: 10.1016/j.gaitpost.2013.10.020.

Kalume, F. et al. (2007) 'Reduced sodium current in Purkinje neurons from Nav1.1 mutant mice: Implications for ataxia in severe myoclonic epilepsy in infancy', Journal of Neuroscience, 27(41), pp. 11065–11074. doi: 10.1523/JNEUROSCI.2162-07.2007.

Kawamura, C. M. et al. (2007) 'Comparison between visual and three-dimensional gait analysis in patients with spastic diplegic cerebral palsy', Gait Posture, 25(1), pp. 18–24. doi: 10.1016/j.gaitpost.2005.12.005.

Kedem, P. and Scher, D. M. (2016) 'Evaluation and management of crouch gait', Current Opinion in Pediatrics, 28(1), pp. 55–59. doi: 10.1097/MOP.0000000000000316.

Kim, H. et al. (2016) 'Relations among motor, social, and cognitive skills in pre-kindergarten children with developmental disabilities', Res Dev Disabil. 2016/02/08, 53–54, pp. 43–60. doi: 10.1016/j.ridd.2016.01.016.

Knupp, K. G. et al. (2017) 'Parental Perception of Comorbidities in Children With Dravet Syndrome', Pediatric Neurology. Elsevier Inc., 76, pp. 60–65. doi: 10.1016/j.pediatrneurol.2017.06.008.

van der Krogt, M. M., Delp, S. L. and Schwartz, M. H. (2012) 'How robust is human gait to muscle weakness?', Gait and Posture. Elsevier B.V., 36(1), pp. 113–119. doi: 10.1016/j.gaitpost.2012.01.017.

Lagae, L. et al. (2018) 'Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey', Developmental Medicine and Child Neurology, 60(1), pp. 63–72. doi:

10.1111/dmcn.13591.

Lagae, L. et al. (2019) 'Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial', The Lancet. Elsevier Ltd, 394(10216), pp. 2243–2254. doi: 10.1016/S0140-6736(19)32500-0.

de Lange, I. M.-L. et al. (2019) 'Outcomes and comorbidities of SCN1A-related seizure disorders', Epilepsy and Behavior. The Authors, 90, pp. 252–259. doi: 10.1016/j.yebeh.2018.09.041.

Leardini, A. et al. (2019) 'Multi-segment foot models and their use in clinical populations', Gait and Posture. Elsevier, 69, pp. 50–59. doi: 10.1016/j.gaitpost.2019.01.022.

Lee, K. J. et al. (2014) 'The effects of a balance exercise program for enhancement of gait function on temporal and spatial gait parameters in young people with intellectual disabilities', J Phys Ther Sci. 2014/04/26, 26(4), pp. 513–516. doi: 10.1589/jpts.26.513.

Lee, K., Lee, M. and Song, C. (2016) 'Balance training improves postural balance, gait, and functional strength in adolescents with intellectual disabilities: Single-blinded, randomized clinical trial', Disabil Health J. 2016/03/16. Elsevier Inc, 9(3), pp. 416–422. doi: 10.1016/j.dhjo.2016.01.010.

Liberati, A. et al. (2009) 'The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration', PLoS Med, 6(7), p. e1000100. doi: 10.1371/journal.pmed.1000100.

Lydersen, S. et al. (2007) 'Choice of test for association in small sample unordered r x c tables', 26, pp. 4328–4343. doi: 10.1002/sim.2839.

MacKinnon, C. D. (2018) Sensorimotor anatomy of gait, balance, and falls, Handbook of Clinical Neurology. doi: 10.1016/B978-0-444-63916-5.00001-X.

Mahony, K. et al. (2009) 'Inter-tester reliability and precision of manual muscle testing and hand-held dynamometry in lower limb muscles of children with spina bifida', Physical and Occupational Therapy in Pediatrics, 29(1), pp. 44–59. doi: 10.1080/01942630802574858.

Maïano, C., Hue, O. and April, J. (2019) 'Effects of motor skill interventions on fundamental movement skills in children and adolescents with intellectual disabilities: a systematic review', Journal of Intellectual Disability Research, 63(9), pp. 1163–1179. doi: 10.1111/jir.12618.

Malatesta, D. et al. (2013) 'Effect of obesity onset on pendular energy transduction at spontaneous walking speed: Prader-willi versus nonsyndromal obese individuals', Obesity, 21(12), pp. 586–591. doi: 10.1002/oby.20455.

Di Marco, R. et al. (2016) 'Concurrent repeatability and reproducibility analyses of four marker placement protocols for the foot-ankle complex', Journal of Biomechanics. Elsevier, 49(14), pp. 3168–3176. doi: 10.1016/j.jbiomech.2016.07.041.

Di Marco, R. et al. (2019) 'Gait abnormalities in people with Dravet syndrome: A cross-sectional multi-center study', European Journal of Paediatric Neurology. Elsevier Ltd, 23(6), pp. 808–818. doi: 10.1016/j.ejpn.2019.09.010.

McGinley, J. L. et al. (2009) 'The reliability of three-dimensional kinematic gait measurements: a systematic review', Gait Posture, 29(3), pp. 360–369. doi: 10.1016/j.gaitpost.2008.09.003.

McPoil, T. G. et al. (1999) 'Variability of plantar pressure data: A comparison of the two-step and midgait methods', Journal of the American Podiatric Medical Association, 89(10), pp. 495–501. doi: 10.7547/87507315-89-10-495.

Molenaar, H. M. et al. (2008) 'Age-specific reliability of two grip-strength dynamometers when used by children', Journal of Bone and Joint Surgery - Series A, 90(5), pp. 1053–1059. doi: 10.2106/JBJS.G.00469.

Mudge, A. J. et al. (2014) 'Normative reference values for lower limb joint range, bone torsion, and alignment in children aged 4-16 years', Journal of Pediatric Orthopaedics Part B, 23(1), pp. 15–25. doi: 10.1097/BPB.0b013e328364220a.

Mudge, A. J. et al. (2019) 'Can pedobarography predict the occurrence of heel rocker in children with lower limb spasticity?', Clinical Biomechanics. Elsevier, 71(November 2018), pp. 208–213. doi: 10.1016/j.clinbiomech.2019.10.022.

Muro-de-la-Herran, A. et al. (2014) 'Gait analysis methods: an overview of wearable and non-wearable systems, highlighting clinical applications', Sensors (Basel), 14(2), pp. 3362–3394. doi: 10.3390/s140203362.

Nabbout, R. et al. (2013) 'Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy', Orphanet Journal of Rare Diseases, 8(1), pp. 1–8. doi: 10.1186/1750-1172-8-176.

Nieuwenhuys, A. et al. (2016) 'Identification of joint patterns during gait in children with cerebral palsy: a Delphi consensus study', Developmental Medicine & Child Neurology, 58(3), pp. 306–313. doi: 10.1111/dmcn.12892.

Novacheck, T. F. and Gage, J. R. (2007) 'Orthopedic management of spasticity in cerebral palsy.', Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery, 23(9), pp. 1015–1031. doi: 10.1007/s00381-007-0378-6.

O'Keefe, J. A. et al. (2014) 'Implementation of a markerless motion analysis method to quantify hyperkinesis in males with fragile X syndrome', Gait Posture. 2013/11/21, 39(2), pp. 827–830. doi: 10.1016/j.gaitpost.2013.10.017.

O'Keefe, J. A. et al. (2016) 'Gait and Functional Mobility Deficits in Fragile X-Associated Tremor/Ataxia Syndrome', Cerebellum. 2015/08/25. The Cerebellum, 15(4), pp. 475–482. doi: 10.1007/s12311-015-0714-4.

O'Sullivan, R. et al. (2018) 'The natural history of crouch gait in bilateral cerebral palsy: A systematic review', Research in Developmental Disabilities. Elsevier, 80(October 2017), pp. 84–92. doi: 10.1016/j.ridd.2018.06.013.

Ong, A. M. L., Hillman, S. J. and Robb, J. E. (2008) 'Reliability and validity of the Edinburgh Visual Gait Score for cerebral palsy when used by inexperienced observers', Gait Posture, 28(2), pp. 323–326. doi: 10.1016/j.gaitpost.2008.01.008.

De Onis, M. and Lobstein, T. (2010) 'Defining obesity risk status in the general childhood population: Which cut-offs should we use?', International Journal of Pediatric Obesity, 5(6), pp. 458–460. doi: 10.3109/17477161003615583.

Oppewal, A. et al. (2014) 'Physical fitness is predictive for a decline in daily functioning in older adults with intellectual disabilities: results of the HA-ID study', Res Dev Disabil. 2014/06/21, 35(10), pp. 2299–2315. doi: 10.1016/j.ridd.2014.05.027.

Oppewal, A. et al. (2015) 'Physical fitness is predictive for a decline in the ability to perform instrumental activities of daily living in older adults with intellectual disabilities: Results of the HA-ID study', Res Dev Disabil. 2015/06/17, 41–42, pp. 76–85. doi: 10.1016/j.ridd.2015.05.002.

Oppewal, A., Festen, D. A. M. M. and Hilgenkamp, T. I. M. M. (2018) 'Gait Characteristics of Adults With Intellectual Disability', Am J Intellect Dev Disabil. 2018/04/20, 123(3), pp. 283–299. doi: 10.1352/1944-

7558-123.3.283.

Oppewal, A. and Hilgenkamp, T. I. M. M. (2017) 'The dual task effect on gait in adults with intellectual disabilities: is it predictive for falls?', Disabil Rehabil. 2017/09/05. Informa UK Ltd., 41(1), pp. 1–7. doi: 10.1080/09638288.2017.1370730.

Oppewal, A. and Hilgenkamp, T. I. M. M. (2018) 'The association between gait and physical fitness in adults with intellectual disabilities', Journal of Intellectual Disability Research. 2018/03/27, 62(5), pp. 454–466. doi: 10.1111/jir.12484.

Pataky, T. C. (2010) 'Generalized n-dimensional biomechanical field analysis using statistical parametric mapping', Journal of Biomechanics. Elsevier, 43(10), pp. 1976–1982. doi: 10.1016/j.jbiomech.2010.03.008.

Pataky, T. C., Robinson, M. A. and Vanrenterghem, J. (2013) 'Vector field statistical analysis of kinematic and force trajectories', Journal of Biomechanics. Elsevier, 46(14), pp. 2394–2401. doi: 10.1016/j.jbiomech.2013.07.031.

Perry, J. and Burnfield, J. M. (2010) Gait analysis: normal and pathological function. 2nd edn. SLACK Incorporated.

Peters, M. J. H. et al. (2011) 'Revised normative values for grip strength with the Jamar dynamometer', Journal of the Peripheral Nervous System, 16(1), pp. 47–50. doi: 10.1111/j.1529-8027.2011.00318.x.

Petraglia, F. et al. (2018) 'Inertial sensors versus standard systems in gait analysis: a systematic review and meta-analysis', Eur J Phys Rehabil Med, 55(2), pp. 265–280. doi: 10.23736/S1973-9087.18.05306-6.

Pinzone, O., Schwartz, M. H. and Baker, R. W. (2016) 'Comprehensive non-dimensional normalization of gait data', Gait and Posture. Elsevier B.V., 44, pp. 68–73. doi: 10.1016/j.gaitpost.2015.11.013.

Ploegmakers, J. J. W. et al. (2013) 'Grip strength is strongly associated with height, weight and gender in childhood: A cross sectional study of 2241 children and adolescents providing reference values', Journal of Physiotherapy. Elsevier, 59(4), pp. 255–261. doi: 10.1016/S1836-9553(13)70202-9.

Rancho Los Amigos National Rehabilitation Center (2001) Observational gait analysis handbook. 4a ed. Downey: Los Amigos Research and Education Institute Incorporate.

Rathinam, C. et al. (2014) 'Observational gait assessment tools in paediatrics--a systematic review', Gait Posture, 40(2), pp. 279–285. doi: 10.1016/j.gaitpost.2014.04.187.

Read, H. S. et al. (2003) 'Edinburgh visual gait score for use in cerebral palsy', Journal of Pediatric Orthopaedics, 23(3), pp. 296–301. doi: 10.1097/00004694-200305000-00005.

Redmond, A. C., Crane, Y. Z. and Menz, H. B. (2008) 'Normative values for the Foot Posture Index', Journal of Foot and Ankle Research, 1(1), pp. 1–9. doi: 10.1186/1757-1146-1-6.

Ricci, D. et al. (2015) 'A prospective longitudinal study on visuo-cognitive development in Dravet syndrome: Is there a "dorsal stream vulnerability"?', Epilepsy Research. Elsevier B.V., 109(1), pp. 57–64. doi: 10.1016/j.eplepsyres.2014.10.009.

Richardson, W. S. et al. (1995) 'The well-built clinical question: a key to evidence-based decisions', ACP J Club, 123(3), pp. A12-3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7582737.

Rilstone, J. J. et al. (2012) 'Dravet syndrome: Seizure control and gait in adults with different SCN1A mutations', Epilepsia, 53(8), pp. 1421–1428. doi: 10.1111/j.1528-1167.2012.03583.x.

Rodda, J. M. et al. (2004) 'Sagittal gait patterns in spastic diplegia', Journal of Bone and Joint Surgery - Series B, 86(2), pp. 251–258. doi: 10.1302/0301-620X.86B2.13878.

Rodda, J. M. et al. (2012) 'Progressive gait deterioration in adolescents with Dravet syndrome', Archives of Neurology, 69(7), pp. 873–878. doi: 10.1001/archneurol.2011.3275.

Rogozinski, B. M. et al. (2009) 'The efficacy of the floor-reaction ankle-foot orthosis in children with cerebral palsy', Journal of Bone and Joint Surgery - Series A, 91(10), pp. 2440–2447. doi: 10.2106/JBJS.H.00965.

Romkes, J. et al. (2007) 'Evaluating upper body movements during gait in healthy children and children with diplegic cerebral palsy', Journal of Pediatric Orthopaedics Part B, 16(3), pp. 175–180. doi: 10.1097/BPB.0b013e32801405bf.

Rothera, I. et al. (2002) 'Ageing and the nigrostriatal dopaminergic system', Int J Geriatr Psychiatry, 17(4), pp. 359–370. doi: 10.1002/gps.606.

Rozumalski, A. and Schwartz, M. H. (2009) 'Crouch gait patterns defined using k-means cluster analysis are related to underlying clinical pathology', Gait and Posture, 30(2), pp. 155–160. doi: 10.1016/j.gaitpost.2009.05.010.

Sala, D. A. and Cohen, E. (2013) 'Gait component changes observed during independent ambulation in young children', Indian Journal of Pediatrics, 80(5), pp. 397–403. doi: 10.1007/s12098-012-0926-2.

Salami, F. et al. (2014) 'Mechanical energy assessment of adult with Down syndrome during walking with obstacle avoidance', Res Dev Disabil. 2014/05/06. Elsevier Ltd., 35(8), pp. 1856–1862. doi: 10.1016/j.ridd.2014.04.012.

Salb, J. et al. (2017) 'Gait Analysis in Adults with Intellectual Disabilities Living in a Residential Facility', J Appl Res Intellect Disabil. 2015/10/23, 30(1), pp. 205–210. doi: 10.1111/jar.12227.

Samanta, D. (2020) 'Changing Landscape of Dravet Syndrome Management: An Overview', Neuropediatrics, 51(02), pp. 135–145. doi: 10.1055/s-0040-1701694.

Sandau, M. et al. (2014) 'Markerless motion capture can provide reliable 3D gait kinematics in the sagittal and frontal plane', Medical Engineering and Physics. Institute of Physics and Engineering in Medicine, 36(9), pp. 1168–1175. doi: 10.1016/j.medengphy.2014.07.007.

Scheffer, I. E. (2012) 'Diagnosis and long-term course of Dravet syndrome', European Journal of Paediatric Neurology. Elsevier Ltd, 16(SUPPL. 1), p. S5. doi: 10.1016/j.ejpn.2012.04.007.

Scheffer, I. E. et al. (2017) 'ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology', Epilepsia, 58(4), pp. 512–521. doi: 10.1111/epi.13709.

Scheffer, I. E. and Nabbout, R. (2019) 'SCN1A-related phenotypes: Epilepsy and beyond', Epilepsia, 60(S3), pp. S17–S24. doi: 10.1111/epi.16386.

Schoonjans, A.-S. et al. (2017) 'Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit-risk profile in a new patient population', Current Medical Research and Opinion, 33(10), pp. 1773–1781. doi: 10.1080/03007995.2017.1355781.

Schwartz, M. H. and Rozumalski, A. (2008) 'The gait deviation index: A new comprehensive index of gait pathology', Gait and Posture, 28(3), pp. 351–357. doi: 10.1016/j.gaitpost.2008.05.001.

Schwartz, S. et al. (1992) 'Relationship between two measures of upper extremity strength: Manual muscle test compared to hand-held myometry', Archives of Physical Medicine and Rehabilitation, 73(11), pp. 1063–1068. doi: 10.5555/uri:pii:000399939290172S.

Shieh, W. Y. et al. (2016) 'Stair-Walking Performance in Adolescents with Intellectual Disabilities', Sensors (Basel). 2016/07/15, 16(7). doi: 10.3390/s16071066.

Sinoo, C. et al. (2019) 'Behavior problems and health-related quality of life in Dravet syndrome', Epilepsy and Behavior. Elsevier Inc., 90, pp. 217–227. doi: 10.1016/j.yebeh.2018.11.029.

Smits-Engelsman, B. and Hill, E. L. (2012) 'The relationship between motor coordination and intelligence across the IQ range', Pediatrics. 2012/09/19, 130(4), pp. e950-6. doi: 10.1542/peds.2011-3712.

Spagnolo, E. et al. (2016) 'Gait patterns in Dravet syndrome: Preliminary data of a multicentric longitudinal prospective study', Gait & Posture. Elsevier B.V., 49(September), pp. S10–S11. doi: 10.1016/j.gaitpost.2016.07.037.

Spann, M. N. et al. (2014) 'Morphological features of the neonatal brain support development of subsequent cognitive, language, and motor abilities', Hum Brain Mapp. 2014/03/13, 35(9), pp. 4459–4474. doi: 10.1002/hbm.22487.

Stark, T. et al. (2011) 'Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: A systematic review', PM and R. Elsevier Inc., 3(5), pp. 472–479. doi: 10.1016/j.pmrj.2010.10.025.

Steele, K. M. et al. (2012) 'How much muscle strength is required to walk in a crouch gait?', Journal of Biomechanics. Elsevier, 45(15), pp. 2564–2569. doi: 10.1016/j.jbiomech.2012.07.028.

Stratford, P. W. and Balsor, B. E. (1994) 'A Comparison of Make and Break Tests Using a Hand-Held Dynamometer and the Kin-Com', 19(I).

Sutherland, D. (1997) 'The development of mature gait', Gait and Posture, 6(2), pp. 163–170. doi: 10.1016/S0966-6362(97)00029-5.

Sutherland, D. and Davids, J. R. (1993) 'Common Gait Abnormalities of the Knee in Cerebral Palsy', Clinical Orthopaedics and Related Research, 288, pp. 139–147.

Theologis, T. (2013) 'Lever arm dysfunction in cerebral palsy gait', Journal of Children's Orthopaedics, 7(5), pp. 379–382. doi: 10.1007/s11832-013-0510-y.

Theologis, T. and Wright, J. (2015) 'Is 3-D gait analysis essential? By Professor James Wright. Introduction by Mr. Tim Theologis.', Gait and Posture, 42(3), pp. 227–229. doi: 10.1016/j.gaitpost.2015.05.018.

Thompson, N. et al. (2011) 'Muscle strength and walking ability in Diplegic Cerebral Palsy: Implications for assessment and management', Gait and Posture. Elsevier B.V., 33(3), pp. 321–325. doi: 10.1016/j.gaitpost.2010.10.091.

Toro, B., Nester, C. and Farren, P. (2003) 'A review of observational gait assessment in clinical practice', Physiother Theor Pract, 19, pp. 123–149. doi: 10.1080/0959398039221901.

Vereniging Klinische Genetica Nederland (2019) 'Richtlijn Dravetsyndroom'. Available at: https://richtlijnendatabase.nl/richtlijn/dravetsyndroom/startpagina_-_dravetsyndroom.html.

Verheyen, K. et al. (2018) 'P 055 - Gait Profile Scores indicate that gait deviations in children and young adults with Dravet Syndrome mainly manifest in transverse plane', Gait & Posture, 65, pp. 323–324. doi: https://doi.org/10.1016/j.gaitpost.2018.06.208.

Verheyen, K., Wyers, L., et al. (2019) 'Is standardized video gait analysis a valid alternative for instrumented gait analysis in children with Dravet syndrome?', Gait & Posture, 73, pp. 452–453. doi: https://doi.org/10.1016/j.gaitpost.2019.07.185.

Verheyen, K., Verbecque, E., et al. (2019) 'Motor development in children with Dravet syndrome', Developmental Medicine & Child Neurology, 61(8), pp. 950–956. doi: 10.1111/dmcn.14147.

Verlinden, V. J. et al. (2014) 'Cognition and gait show a distinct pattern of association in the general population', Alzheimers Dement. 2013/07/16, 10(3), pp. 328–335. doi: 10.1016/j.jalz.2013.03.009.

Verschuren, O. et al. (2008) 'Reliability of hand-held dynamometry and functional strength tests for the lower extremity in children with Cerebral Palsy', Disability and Rehabilitation, 30(18), pp. 1358–1366. doi: 10.1080/09638280701639873.

Viehweger, E. et al. (2010) 'Influence of clinical and gait analysis experience on reliability of observational gait analysis (Edinburgh Gait Score Reliability)', Ann Phys Rehabil Med, 53(9), pp. 535–546. doi: 10.1016/j.rehab.2010.09.002.

Villas, N., Meskis, M. A. and Goodliffe, S. (2017) 'Dravet syndrome: Characteristics, comorbidities, and caregiver concerns', Epilepsy and Behavior. The Authors, 74, pp. 81–86. doi: 10.1016/j.yebeh.2017.06.031.

Vuijk, P. J. et al. (2010) 'Motor performance of children with mild intellectual disability and borderline intellectual functioning', J Intellect Disabil Res. 2010/09/22, 54(11), pp. 955–965. doi: 10.1111/j.1365-2788.2010.01318.x.

Whittle, M. W. (1996) 'Clinical gait analysis: A review', Human Movement Science, 15(3), pp. 369–387. doi: 10.1016/0167-9457(96)00006-1.

Wind, A. E. et al. (2010) 'Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults?', European Journal of Pediatrics, 169(3), pp. 281–287. doi: 10.1007/s00431-009-1010-4.

Winter, D. A. (1980) 'Overall principle of lower limb support during stance phase of gait', J. Biomechanics, 13, pp. 923–927.

Winter, D. A. (1983) 'Biomechanical Motor Patterns in Normal Walking', Journal of Motor Behavior, 15(4), pp. 302–330.

Winter, D. A. and Eng, P. (1995) 'Kinetics: our window into the goals and strategies of the central nervous system', Behavioural Brain Research, 67(2), pp. 111–120. doi: 10.1016/0166-4328(94)00154-8.

Wirrell, E. C. et al. (2017) 'Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel', Pediatric Neurology. Elsevier Inc, 68, pp. 18-34.e3. doi: 10.1016/j.pediatrneurol.2017.01.025.

Wolff, M., Cassé-Perrot, C. and Dravet, C. (2006) 'Severe myoclonic epilepsy of infants (Dravet syndrome): Natural history and neuropsychological findings', Epilepsia, 47(SUPPL. 2), pp. 45–48. doi: 10.1111/j.1528-1167.2006.00688.x.

Wondra, V. C., Pitetti, K. H. and Beets, M. W. (2007) 'Gait Parameters in Children with Motor Disabilities Using an Electronic Walkway System: Assessment of Reliability', Pediatric Physical Therapy, 19(4), pp. 326–331. doi: 10.1097/PEP.0b013e3181577d6d.

World Health Organization (2001) 'Internationcal classification of functioning, disability and health: ICF'. Available at: https://apps.who.int/iris/handle/10665/42407.

Wouters, M. et al. (2017) 'Feasibility and reliability of tests measuring health-related physical fitness in children with moderate to severe levels of intellectual disability', American Journal on Intellectual and Developmental Disabilities, 122(5), pp. 422–438. doi: 10.1352/1944-7558-122.5.422.

Wren, T. A. L. et al. (2011) 'Efficacy of clinical gait analysis: A systematic review', Gait and Posture, 34(2), pp. 149–153. doi: 10.1016/j.gaitpost.2011.03.027.

Wren, T. A. L., Rethlefsen, S. and Kay, R. M. (2005) 'Prevalence of Specific Gait Abnormalities in Children With Cerebral Palsy', Journal of Pediatric Orthopaedics, 25(1), pp. 79–83. doi: 10.1097/01241398-200501000-00018.

Wu, Y. W. et al. (2015) 'Incidence of dravet syndrome in a US population', Pediatrics, 136(5), pp. e1310–e1315. doi: 10.1542/peds.2015-1807.

Wuang, Y. P. et al. (2013) 'Test-retest reliabilities of hand-held dynamometer for lower-limb muscle strength in intellectual disabilities', Research in Developmental Disabilities. Elsevier Ltd, 34(8), pp. 2281–2290. doi: 10.1016/j.ridd.2013.04.010.

Wyers, L. et al. (2017) 'O34: Case- control study to identify deviations in gait and physical examination in children and adolescents with Dravet syndrome', Gait & Posture. doi: 10.1016/j.gaitpost.2017.06.288.

Wyers, L., Van de Walle, P., Verheyen, K., et al. (2019a) 'Deviations in gait kinetics in children and adolescents with Dravet Syndrome', Gait & Posture, 73, pp. 52–53. doi: https://doi.org/10.1016/j.gaitpost.2019.07.026.

Wyers, L., Van de Walle, P., Hoornweg, A., et al. (2019) 'Gait deviations in patients with dravet syndrome: A systematic review', European Journal of Paediatric Neurology. Elsevier Ltd, 23(3), pp. 357–367. doi: 10.1016/j.ejpn.2019.03.003.

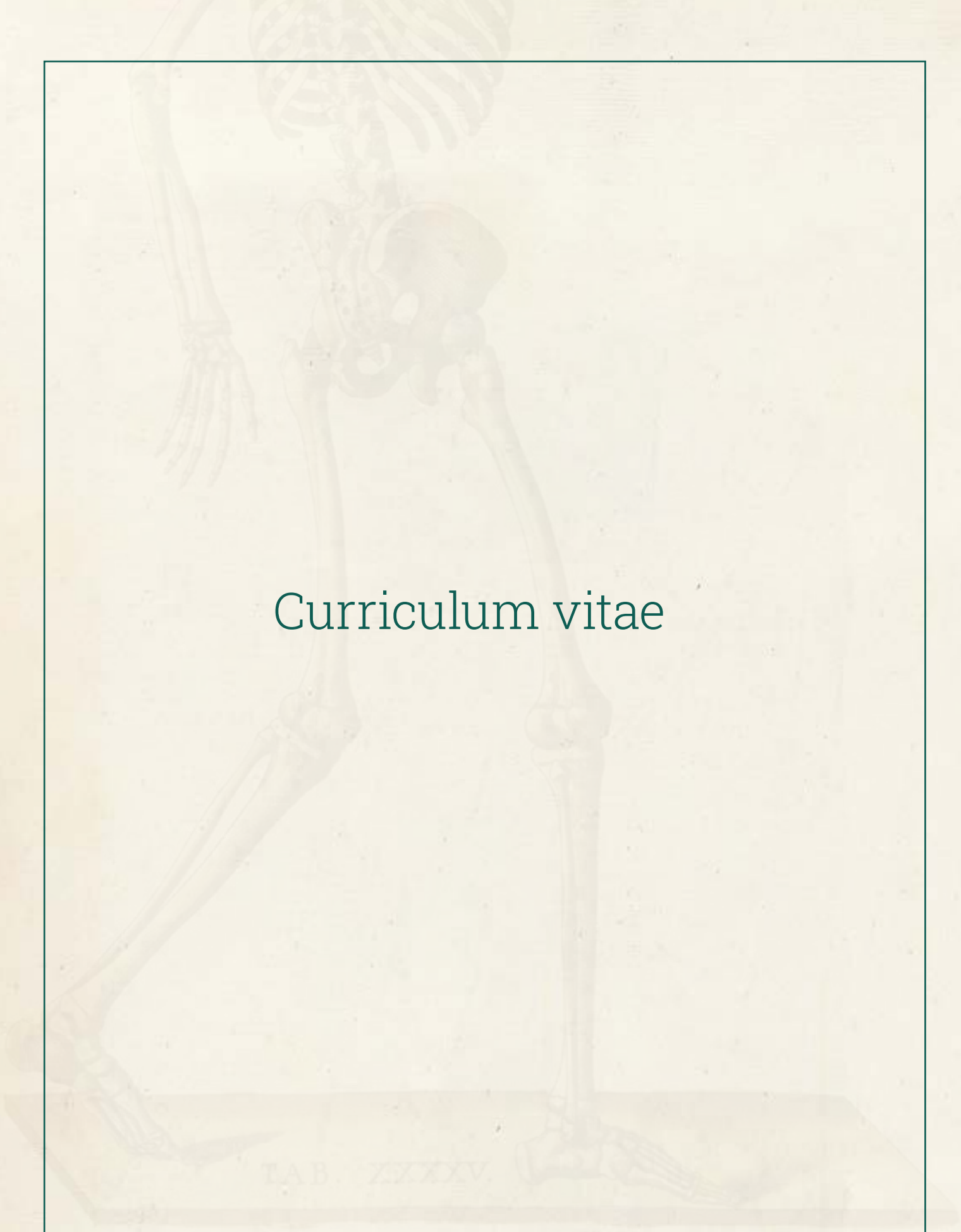
Wyers, L., Van de Walle, P., Verheyen, K., et al. (2019b) 'Lever arm dysfunction in children and adolescents with Dravet Syndrome', Gait & Posture, 73, pp. 465–466. doi: https://doi.org/10.1016/j.gaitpost.2019.07.187.

Wyers, L., Verheyen, K., et al. (2019) 'Neuromechanical control of the lower limb joints during gait in children and adolescents with Dravet Syndrome', Gait & Posture, 73, pp. 158–159. doi: https://doi.org/10.1016/j.gaitpost.2019.07.082.

Yaguramaki, N. and Kimura, T. (2002) 'Acquirement of stability and mobility in infant gait', Gait and Posture, 16(1), pp. 69–77. doi: 10.1016/S0966-6362(01)00205-3.

Ziobro, J. et al. (2018) 'Current Treatment Strategies and Future Treatment Options for Dravet Syndrome', Current Treatment Options in Neurology. Current Treatment Options in Neurology, 20(12). doi: 10.1007/s11940-018-0537-y.

Curriculum vitae



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3. Publications

3.1 Journal articles as first author

Foot-floor contact pattern in children and adults with Dravet Syndrome

Wyers Lore, Di Marco Roberto, Zambelli Stefano, Masiero Stefano, Hallemans Ann, Van de Walle Patricia, Desloovere Kaat, Del Felice Alessandra

Gait and posture - ISSN 0966-6362 - 84(2021), p. 315-320, dio: doi.org/10.1016/J.GAITPOST.2020.12.030
[c:irua:174657]

The mechanics behind gait problems in patients with Dravet Syndrome

Wyers Lore, Verheyen Karen, Ceulemans Berten, Schoonjans An-Sofie, Desloovere Kaat, Van de Walle Patricia, Hallemans Ann

Gait and posture - ISSN 0966-6362 - 84(2021), p. 321-328, doi: doi.org/10.1016/J.GAITPOST.2020.12.029
[c:irua:174656]

Gait deviations in patients with Dravet syndrome: A systematic review

Wyers Lore, Van de Walle Patricia, Hoornweg Aurelie, Tepes Bobescu Ionela, Verheyen Karen, Ceulemans Berten, Schoonjans An-Sofie, Desloovere Kaat, Hallemans Ann

European journal of paediatric neurology - ISSN 1090-3798 - 23:3(2019), p. 357-367 , doi: doi.org/10.1016/J.EJPN.2019.03.003
[c:irua:161392]

3.2 Journal articles as co-author

Normal aging affects unconstrained three-dimensional reaching against gravity with reduced vertical precision and increased co-contraction

Wittenberg George F., Tian Jing, Kortzorg Nick, Wyers Lore, Van Halewyck Florian, Boisgontier Matthieu P., Levin Oron, Swinnen Stephan P., Jonkers Ilse

bioRxiv 2020.12.03.410001; doi: https://doi.org/10.1101/2020.12.03.410001
[Preprint]

Regional and age-dependent Effects of Cortical Magnetic Stimulation on Unconstrained Reaching Behavior

Urbin Mike A., Tian Jing, McKernan Gina P., Kortzorg Nick, Wyers Lore, Van Halewyck Florian, Boisgontier Matthieu P., Levin Oron, Swinnen Stephan P., Jonkers Ilse, Wittenberg George F.

bioRxiv 2020.12.14.422725, doi: doi.org/10.1101/2020.12.14.422725
[Preprint]

Independent walking and cognitive development in preschool children with Dravet syndrome

Verheyen Karen, Wyers Lore, Del Felice Alessandra, Schoonjans An-Sofie, Ceulemans Berten, Van de Walle Patricia, Hallemans Ann

Developmental Medicine & Child Neurology, ISSN 0012-1622 – 63(2020), p. 472-479 , doi: doi.org/10.1111/DMCN.14738
[c:irua:173444]

Clinical usefulness and challenges of instrumented motion analysis in patients with intellectual disabilities

Hallemans Ann, Van de Walle Patricia, Wyers Lore, Verheyen Karen, Schoonjans An-Sofie, Desloovere Kaat, Ceulemans Berten

Gait and posture - ISSN 0966-6362 - 71(2019), p. 105-115, doi: doi.org/10.1016/J.GAITPOST.2019.04.016
[c:irua:161363]

3.3 Conference proceedings as first author

Deviations in gait kinetics in children and adolescents with Dravet Syndrome

Wyers Lore, Van de Walle Patricia, Verheyen Karen, Ceulemans Berten, Schoonjans An-Sofie, Desloovere Kaat, Hallemans Ann

Gait and Posture. 73 (2019) 52–53. doi:10.1016/j.gaitpost.2019.07.026.

Lever arm dysfunction in children and adolescents with Dravet Syndrome

Wyers Lore, Van de Walle Patricia, Verheyen Karen, Ceulemans Berten, Schoonjans An-Sofie, Desloovere Kaat, Hallemans Ann

Gait and Posture. 73 (2019) 465–466. doi: doi.org/10.1016/j.gaitpost.2019.07.187.

Neuromechanical control of the lower limb joints during gait in children and adolescents with Dravet Syndrome

Wyers Lore, Van de Walle Patricia, Verheyen Karen, Ceulemans Berten, Schoonjans An-Sofie, Desloovere Kaat, Hallemans Ann

Gait and Posture. 73 (2019) 158–159. doi: doi.org/10.1016/j.gaitpost.2019.07.082.

O 094–Paediatric reference data are needed to calculate Gait Profile Scores in children, regardless width of age categories

Wyers Lore, Verheyen Karen, Van Criekinge Tamaya, Papageorgiou Eirini, Goudriaan Marije, Desloovere Kaat, Hallemans Ann, Van de Walle Patricia

Gait and Posture. 65 (2018) 191–193. doi: doi.org/10.1016/j.gaitpost.2018.06.129.

O34: Case- control study to identify deviations in gait and physical examination in children and adolescents with Dravet syndrome

Wyers Lore, Van de Walle Patricia, Verheyen Karen, Ceulemans Berten, Schoonjans An-Sofie, Desloovere Kaat, Hallemans Ann

Gait and Posture. (2017). doi:10.1016/j.gaitpost.2017.06.288.

3.4 Conference proceedings as co-author

Does instrumented gait analysis add clinical value in children with severe intellectual disabilities?

Van de Walle Patricia, Ceulemans Berten, Schoonjans An-Sofie, Verheyen Karen, Wyers Lore, Desloovere Kaat, Hallemans Ann

Gait and Posture. 73 (2019) 368–369. doi: doi.org/10.1016/j.gaitpost.2019.07.229.

P 055 - Gait Profile Scores indicate that gait deviations in children and young adults with Dravet Syndrome mainly manifest in transverse plane

Verheyen Karen, Wyers Lore, Hoornweg Aurelie, Tepes Bobescu Ionela, Op De Beeck Nele, Schoonjans An-Sofie, Ceulemans Berten, Hallemans Ann, Van de Walle Patricia

Gait and Posture. 65 (2018) 323–324. doi: doi.org/10.1016/j.gaitpost.2018.06.208.

Is standardized video gait analysis a valid alternative for instrumented gait analysis in children with Dravet syndrome?

Verheyen Karen, Wyers Lore, Cornelissen Kaat, De Swert Stephanie, Schoonjans An-Sofie, Ceulemans Berten, Van de Walle Patricia, Hallemans Ann

Gait and Posture. 73 (2019) 452–453. doi:10.1016/j.gaitpost.2019.07.185.

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University of Antwerp

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Research group MOVANT

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