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# Multimodal evaluation of gait alterations in persons with multiple sclerosis

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# Remerciements

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« Measure what can be measured and make measurable what cannot be measured ».

*Galileo Galiliei*


« If there is a dictum, it would be that it is all a matter of being in the right place,

At the right time,

With the right mentor ».

*C. Miller Fisher*

**For those with a hand in their cap.**

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# Abstract

Gait impairment is a frequent manifestation of multiple sclerosis and is of the utmost functional importance for those who live with this chronic inflammatory neurological condition. It is also a useful clinical outcome measure, usually evaluated on the basis of walking speed measured on a short distance.

In this work, our first hypothesis is that walking speed is a construct significantly influenced by several confounders. Through the use of conventional methods to test gait, we successively address the importance of the distance (and hence locomotor fatigability, first on 100 and next on 500 metres), acceleration capacity and type of walk instructed to the subject. We show that the Timed 25 foot walk test suffer from several shortcomings related to each of these factors. We demonstrate that these are differentially affected in persons with multiple sclerosis as compared to healthy subjects, representing potential individual outcome measures themselves.

Next, our second hypothesis is that walking speed is not the only feature characterizing the gait of persons with multiple sclerosis. We review the different available gait analysis technologies, their application in multiple sclerosis and create a new gait analysis system adapted to our needs. After technical validation, we design 26 gait features in order to capture other dimensions of walk than its speed, such as ataxia. We define those using factorial analysis. Finally, we use this system to explore the variance of gait in a population of healthy subjects and persons with multiple sclerosis. Using a mixed model analysis, we show that while walking speed is the main contributing factor to gait variance in such populations, other dimensions significantly come into play and should be considered in order to fully characterize ambulation in multiple sclerosis.

# Résumé

Les troubles de la marche sont une manifestation fréquente de la sclérose en plaques, d'importance majeure du point de vue fonctionnel pour les personnes qui vivent avec cet affection inflammatoire chronique du système nerveux central. Ils représentent également une mesure de l'impact de la maladie, don't l'évaluation se fonde essentiellement sur la mesure de la vitesse de marche sur courte distance.

Dans ce travail, notre première hypothèse est que la vitesse de marche est un concept sous l'influence significative de plusieurs facteurs. En utilisant des approches conventionnelles pour évaluer la marche, nous étudions successivement l'importance de la distance (et donc de la fatigabilité motrice, d'abord sur 100 puis sur 500 mètres), de la capacité à accélérer et du type de consigne de marche. Nous montrons que ces éléments sont des lacunes insuffisamment prises en compte par le "test de 25 pieds", qu'ils sont spécifiquement influencés par la sclérose en plaques et le handicap qui y est associé, et qu'ils pourraient représenter des mesures cliniques *per se* d'aspects ambulatoires spécifiques.

Notre seconde hypothèse est que la vitesse de marche n'est pas le seul élément permettant de caractériser la marche des personnes présentant une sclérose en plaques. Nous faisons une revue des différentes techniques permettant l'analyse de la marche, de leur utilisation dans le domaine de la sclérose en plaques, et nous proposons la création d'un nouveau système d'analyse de marche adapté à nos besoins. Après une étape de validation technique, nous définissons 26 paramètres de marche dans le but de capter d'autre dimensions de la marche que sa vitesse, comme l'ataxie. Ces définitions sont définies sur base d'une analyse factorielle. Finalement, nous utilisons ce système pour étudier la variance de la marche dans une population de sujets sains et de personnes

présentant une sclérose en plaques. En utilisant une analyse de variance à effets mixtes, nous démontrons que si la vitesse de marche est la composante principale contribuant à la variance de la marche dans une telle population, d'autres dimensions y participent significativement et devraient être prises en compte pour permettre une caractérisation exhaustive de la locomotion, en particulier dans le contexte de la sclérose en plaques.

# 1  Overview of Multiple Sclerosis

## 1.1  Pathophysiology

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) (1). Its main pathological hallmarks are inflammation, demyelination, remyelination, axonal degeneration and glial scar formation occurring either in circumscribed zones (i.e. plaques) or in diffuse areas throughout the brain – both in the gray and the white matter – and the spinal cord (2, 3). The exact pathophysiological mechanisms underlying these changes remain largely elusive, but are increasingly disentangled by scientific works focused on immune dysregulation triggered by a complex interplay between genetic (4) and environmental (5) factors. In MS, there is a loss of immune tolerance to self-antigens (6) characterised by an abnormal activated state of peripheral autoreactive regulatory T lymphocytes that probably develops in several steps, and leads them to transgress the blood brain barrier, creating a local pro-inflammatory environment which in turn allows the entrance of an other wave of T cells from the periphery to the brain parenchyma where they orchestrate a second inflammatory reaction (7). This reaction implies CD4+ and CD8+ T lymphocytes, B lymphocytes, monocytes and macrophages, complement activation and antibody deposition (8). In relapsing forms of MS, acute areas of demyelination mostly in the white matter predominate and are associated with a breakdown of the blood-brain barrier (9). In progressive stages however, diffuse white and gray matter dysfunction associated with axonal degeneration and milder demyelination are observed (10), restricted behind an intact blood-brain barrier.

## 1.2  Clinical manifestations

The clinical manifestations of MS are broad by definition (11), since they are the consequence of several circumscribed demyelinating lesions that can be localised virtually anywhere within the CNS. At the early stages, neurological symptoms will typically include:

- Sensitive negative or positive manifestations (e.g. Lhermitte's sign is highly suggestive of MS) mostly linked to damage of the posterior columns at the level of

the cerebral spinal cord or more rarely to lesions along the supraspinal sensory pathways

- Gait disorders related to either sensory or cerebellar ataxia, or to paraparesis
- Visual impairment reflecting demyelination along the optic pathway, frequently at the level of the optic nerve or very rarely beyond
- pyramidal dysfunction of the lower or upper limbs usually related to corticospinal damage
- Bowel or bladder dysfunction, typical of dysruption autonomic pathways at the level of the spinal cord
- Oculomotor deficits, internuclear ophtalmoplegia being almost pathognomonic, or more rarely other cranial nerve syndromes
- Vertigo, oscillopsia and loss of balance in the context of a central vestibular syndrome or cerebellar involvement

Apart from internuclear ophtalmoparesis, Lhermitte's sign and Uthoff phenomenon, there is no symptom that is clearly specific of MS, and the diagnose always rely on a detailed clinical history and examination, completed most of the time by other investigations (12, 13).

When the disease follows a progressive course, the same symptoms can be observed, with locomotor impairment and mental dysfunctions dominating the clinical picture. The clinical presentation at onset is most frequently a progressive myelopathy (14), and early detection of subtle motor symptoms require high clinical skills, repeated evaluations over time and detailed anamnesis. Additionally, other non-specific symptoms may appear, such as fatigue (whether motor or cognitive), pain and mood disorders.

## 1.3 Natural history and clinical subtypes

In 80 to 85% of the population of persons with MS (pwMS), especially in young individuals, the first manifestations of the disease follow a relapsing-remitting (RR) course during several years, with repeated episodes of subacute neurological focal deterioration recovering to a variable extent over weeks to months, separated by lull periods. pwMS who do not experience any additional relapse after a single episode fall within a category termed « clinically isolated syndrome » (CIS). The rate of new relapses per year in most populations of RRMS subjects varies between 0.5 and 1.5, and tend to

decrease over time. Over the years, recovery from relapses becomes increasingly less good, and 30 to 65% of untreated pwMS will enter a secondary progressive (SP) stage (15, 16), where the disability accumulates slowly and insidiously, although at variable rates. A smaller proportion of pwMS – 15 to 20% – will experience a progressive disability from the onset of their symptoms (primary progressive MS) without any acute exacerbation throughout the course of their illness. Very rarely, one or a few close in time relapses will be directly followed by a progressive course, this unusual phenotype being called relapsing progressive MS.

## 1.4 Epidemiology

Incidence and prevalence of MS are geographically heterogeneous, probably because environmental and genetic factors involved in the pathogenesis of the disease are also heterogeneous between populations. In Western Europe, they are recognised as medium to high. Based on epidemiological studies performed in North-Eastern France, prevalence can approximately be inferred to 1.15 for 1000 persons (17) in Belgium, with a female to male ratio of 2.4, typically affecting young adults between 20 and 40 years old. In this population, it is worldwide the most common cause of neurological disability after traumatic brain injury (18). Through the same approximation, the incidence of MS in Belgium over a year is probably around 7.7 to 11 new cases for 100000 habitants.

## 1.5 Care of the person with MS

MS is an incurable chronic disease requiring a life-long management that will generally include in various proportions the intervention of neurologists, psychologists, physical therapists, social workers and more. It is thus largely beyond the scope of the present work to describe the detail of these interventions, and while casting a global outline of pwMS management, we will focus mainly on the aspects to which our contribution might be relevant.

### 1.5.1 Pharmacological therapies

### 1.5.1.1 Relapses therapies

On the basis of several studies performed in the 80's (19, 20), it is now widely accepted that high doses of intravenous methylprednisolone represent the best available option

for pwMS with overt acute relapses, even though the effect seems to be more apparent on the time to recovery than on the magnitude of the recovery itself. Few studies support the use of alternative therapeutic options, such as plasma exchange (21), monoclonal antibodies (22, 23) or intravenous immunoglobulins.

## 1.5.1.2 Disease modifying drugs

Since 1993, drugs that have the potential to alter the course of the disease by reducing the frequency of relapses, the time to confirmed disability and the brain magnetic resonance imaging (MRI) surrogate markers of disease activity have become increasingly available (24-26). These drugs act upon immunological pathways presumed to be involved in the inflammatory component of MS' pathogenesis. Most authors assume that reducing the overall level of CNS inflammation will translate into a reduction of disease flares, i.e. relapses, and will also impact progressive neurodegenerative phenomenon, i.e. disability progression, which are usually quantified by repeated EDSS evaluation and functional measures.

Interferon beta-1b, interferon beta-1a and glatiramer acetate emerged as effective therapies for MS during the 90's through a wealth of fundamental and clinical evidence obtained during the 80's. At present, those 3 drugs are still considered as the basis (« first line » therapies) of MS treatment in most western countries. Their mechanisms of action mainly include inhibition of T-cells costimulation and activation processes, modulation of the balance of anti- and pro-inflammatory cytokines and decrease of aberrant T-cell migration.

In 2005, natalizumab, a monoclonal antibody targeting the $\alpha_4$ subunit of the $\alpha_4\beta_1$ integrin on leukocytes (mainly lymphocytes and monocytes), thereby preventing their entry within the CNS and the intestinal mucosa, was approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA). Given its potent action on clinical relapses and MRI markers of activity compared to placebo (27), natalizumab was considered as a « second line » therapy for pwMS with persisting clinical and radiological disease activity despite a « first line » therapy, or for pwMS with highly active disease from the onset.

In 2011, fingolimod, an oral drug mostly acting through the modulation of the sphingosine 1-phosphate receptor signalling pathway and preventing the egress of peripheral lymphocytes from lymph nodes, was approved by the FDA and the EMA as a

« second line » therapy under the same indications as natalizumab. It was demonstrated that fingolimod was superior to placebo (28) and to interferon beta 1a (29) to decrease the annualized rate of relapse as well as the number of new or enlarged T2 lesions on brain MRI in a population of people with relapsing MS.

In 2012, teriflunomide, an oral drug inhibiting the dihydroorotate dehydrogenase and hence decreasing globally peripheral activated T-cells proliferation, was also approved by the FDA for the treatment of persons with RRMS. Teriflunomide modestly but significantly reduced the annualized relapse rate and the risk of disability progression when compared to placebo (30).

In 2013, BG-12 (dimethyl fumarate) was the third oral drug approved for the relapsing forms of MS. BG-12's putative mechanism of action is anti-inflammatory and cytoprotective effects at the level of the CNS through activation of nuclear 1 factor (erythroid derived 2)-like 2 (Nrf2). Taken orally twice daily it has demonstrated a significant effect on the rate of relapse in two large phase 3 trials (31, 32), performed with and without an active comparator. Only the trial performed without an active comparator (31) demonstrated a significant reduction on disability progression.

All the aforementioned drugs bear potential side effects, which are beyond the scope of this mini-review, but frequently place the individual choice of an MS drug and the evaluation of its benefit-risk ratio at the centre of the discussion between neurologists and pwMS.

Based on previous experience linking the number of relapses in the early course of the disease with the risk of long term disability, and on short to medium term observational studies, early initiation of interferon beta-1a, interferon beta-1b and glatiramer acetate in pwMS with relapsing-remitting disease courses is thought to prevent long term disability as quantified by the Expanded Disability Status Score (EDSS). The same concepts apply to natalizumab and fingolimod, although there is little evidence to support this assumption at the moment. However, according to natural history studies (33), it seems that when a certain degree of disability is reached, regardless of the MS type, progression becomes irreversible.

For pwMS with a secondary progressive disease course, 7 major phase 3 trials evaluating interferon beta, mitoxantrone and intravenous immunoglobulins were performed (34-39). Only one of them (34) showed positive results with a beneficial effect of interferon beta-1b on the primary endpoint which was progression of disability

according to the EDSS. The subgroup analysis revealed that the treatment effect appeared to be more pronounced in pwMS with an active disease, i.e. 2 or more relapses or 1-point change in the EDSS within the 2 years prior to study entry.

There has been less studies in primary progressive MS, although trials investigating interferon beta-1a (40), interferon beta-1b (41), glatiramer acetate (42) and rituximab (43) have been performed. Overall, no significant clinical benefit was observed, except for young pwMS (below 51 year old) displaying baseline gadolinium-enhancing lesion on their MRI scan who were treated with rituximab.

It is thus generally not recommended to initiate pharmacological therapies for persons with progressive forms of MS.

## 1.5.1.3 Treatment of symptoms

There are numerous pharmacological options used to treat the various symptoms of MS, but few have been the subject of rigorous evaluations. The target symptoms mainly include gait disorders and ataxia, tremor, spasticity, neuropathic pain, cognitive dysfunction, chronic fatigue, sleep disorders, bowel and bladder symptoms, psychiatric conditions associated with MS, neuro-ophtalmological disorders and speech disturbances. We will only discuss medication trials performed in the context of gait disorders.

Fampridine or 4-aminopyridine is a drug that has been used for a long time for the treatment of various symptoms in numerous neurological conditions, including Lambert-Eaton myasthenic syndrome and MS (44). Although it acts as a potassium channel blocker and has first been thought to facilitate axonal transmission by prolonging action potentials at the level of demyelinated areas (45, 46), its precise mechanism of action remains unclear (47). More recently, 2 large placebo-controlled randomized trials have investigated the potential of a sustained release form of fampridine to improve walking disorders of pwMS (48, 49). These studies have demonstrated both the efficacy and safety fampridine to treat ambulatory dysfunction in approximately 40% of "responders" pwMS. For instance, a significant change in the chosen primary endpoint, walking speed over a distance of 7.62m, was observed in 35% (48) and 42.9% (49) of the treated populations.

The MUSEC trial evaluated the effect of cannabis extract to relieve muscle stiffness in pwMS (50, 51). A significant favourable change was also observed in walking abilities,

according to a patient-rated scale, namely the MSWS-12. In regard of this outcome measurement, the actual biomechanical impact of cannabinoids on gait disorders of pwMS can only be speculated.

## 1.5.2  Non pharmacological interventions

### 1.5.2.1 Cognitive rehabilitation

Cognitive dysfunction is a frequent and disabling manifestation of MS (52) that can sometimes appear early in the course of the disease. While cognitive abnormalities of pwMS can be diverse, their *primum movens* is generally considered to be impaired processing speed. Cognitive impairment is one of the major factor responsible for a decrease in pwMS' participation to work and social life, at least partly independently from physical disability (53). Neuropsychological rehabilitation has thus emerged as one of the standard of care of cognitively disabled pwMS (54), although formal evidence supporting its effectiveness is still lacking. Some authors also advocate the use of exercise training and increased physical activity as an approach to improve cognitive dysfunction in MS (55).

### 1.5.2.2 Physical therapy

Physical therapy has long been considered as a symptomatic and passive approach, outshined by pharmacological therapies that are still the standard of care in MS. However, there is a growing body of evidence supporting the use of exercise training as an add-on therapy in the care of pwMS (56). Exercise training is defined as a planned, repetitive and structured physical activity undertaken over a long period to maintain or improve physical fitness and functional capacity. It includes aerobic exercise, progressive resistance training and the so-called non-conventional methods (e.g. yoga). Beyond beneficial effects already established on walking ability (57) and quality of life (58),  small evidence is now suggesting a favourable impact of exercise training upon biological (59), brain structural (60) and functional (61) parameters linked to MS pathology. Despite numerous initiatives aimed at coaching pwMS to perform exercise training as a mean to improve their mental and physical well being, the multidimensional nature of the subject has so far kept it out of the reach of proper scientific validation.

Occupational therapy interventions are generally required for pwMS who are more disabled, and includes advising appropriate environmental modifications.

### 1.5.2.3 Psychological management

Psychological support is sometimes advisable over medium to long periods in order to improve the subjective well being of pwMS. Anxiety and depression are prevalent in the pwMS population (62) and need to be managed accordingly, although this assumption lies mainly on clinical experience. No guidelines exist on how, when and for whom psychological management should be considered in MS. Nevertheless, in a population of pwMS treated with first line therapies and with residual radiologically active disease, it was demonstrated that a structured program of stress management therapy was beneficial when compared with the standard treatment (63). Stress management therapy is a psychological concept consisting of explanation by a skilled therapist of methods aimed at improving problem solving aptitudes, relaxation achievement, increasing positive activities, cognitive restructuring and enhancing social support, all pondered according to the subject's profile, and administered in several sessions repeated over time. It is interesting to note that beyond the « obvious » psychological beneficial effects of this approach that remain difficult to quantify, a significant reduction in the MRI activity was also demonstrated in this study (63).

## 1.6 Functional consequences and quality of life in persons with MS

Disability (i.e. loss of function) is at the centre of MS representation, for the society and for health care professionals. This is illustrated by a considerable confusion in the literature between neurological symptoms of MS and the loss of function they may cause. Permanent neurological dysfunction may arise either from incomplete recovery of relapses, or from slow and irreversible accumulation of symptoms in the progressive stages of the disease. Thus, at the individual level, the qualitative nature of the loss of function at the late stage of the disease mirrors, at least from the clinical point of view, the heterogeneous sum of previous clinical manifestations. This clinical picture is usually dominated by gait disorders and cognitive impairment.

From the pwMS point of view, it has been demonstrated that amongst the multiple neurological dysfunctions that could be observed throughout the course of MS, gait disability and visual impairment were the bodily functions considered as the most

important (64). This observation seemed at least partly independent of the duration of the disease.

Finally, disability and quality of life are not strongly correlated (65). This is explained by the implication of other factors usually not taken into account, especially psychological variables difficult to capture and quantify (resilience, mood, coping abilities, psychosocial environment) but also by improper disability measures. It should be stressed that disability, as defined by the World Health Organisation (66) is a complex phenomenon reflecting the interaction between a person's body and the society in which she or he lives. It seems thus perhaps too optimistic to consider a single scale as a valid tool to measure it.

## 1.7 Clinical outcome measures in MS

In clinical sciences, the term « outcome measure » is used to describe a quantitative variable related to the state of a subject in the context of a disease or its consequences. This notion is mostly applied in order to quantify the quality and effectiveness of any type of intervention aimed at modifying the course of an illness and its downstream effects. Amongst the multiple outcome measures that have been designed to fit MS studies, which can be clinical, radiological, electrophysiological or biological, we will concentrate on the former.

MS, because of its multiple clinical manifestations (and because many new pharmacological treatments targeting specific dimensions of the disease have recently appeared), is the subject of a very high number of clinical outcome measures (67). These are often combined in order to better capture one or several specific symptomatic dimensions. Clinical outcome measures are also useful in observational studies, for the assessment of function of specific neurological pathways and their correlation with physiological, radiological or biological markers, in order to further elucidate fundamental mechanisms underlying the pathophysiology of MS. Finally, clinical outcome measures are of paramount importance for the rigorous routine clinical follow-up of pwMS.

Clinical outcome measures can either be obtained by standardized questionnaires (Patient-reported outcome measures) or by clinical observation and measurement (annualized relapse rate, EDSS and MSFC).

### 1.7.1 Patient-reported outcome measures

Although the science of patient-reported outcome measures (PRO) has only been recently endorsed by the MS research and clinical community, it is common sense to admit that the first step to evaluate the impact of a disease on a subject is to include a measure of how she or he feels. This type of approach has however proven to be very difficult because trying to objectively assess a specific component of the multiple dimensions of MS without being influenced by the others leads to complex methodological issues (68). Almost all dimensions of MS have been addressed by one or several PRO scale and it is beyond our goal to review them entirely.

In the field of gait analysis, the most widely acknowledged scale is the 12-Items MS Walking Scale (MSWS-12) (69), which has proven to be reliable, valid and responsive. The MSWS-12 was designed by validating the psychometrics of the 12 items in two large pwMS cohorts. These items were chosen from a 141 items battery based on their relevance towards gait, according to pwMS interviews, experts' opinion and a literature review. After psychometric validation in a large sample of pwMS, the responsiveness of the scale was measured in 2 independent samples: a cohort of persons with relapsing MS experiencing relapses and a cohort of persons with primary progressive MS experiencing progression. The MSWS-12 proved to be more responsive than the Functional Assessment Multiple Sclerosis mobility scale, the 36-Item Short Form Health Physical Functioning scale, the EDSS, the timed-25 foot walk test and Guy's Neurologic disability scale lower limb disability item.

While the MSWS-12 and the majority of PRO, whatever their underlying psychometric qualities, are considered as probably simpler than clinician-based rating scales, we believe that their somehow subjective basis should be kept in mind when interpreting them. Moreover, it should be stressed that these are purely quantitative measures not aimed at further defining the type of global alteration they evaluate, because they are not suited for a qualitative interpretation (e.g. distinguishing ataxia from paresis). The MSWS-12 and other gait-oriented PRO scales are hence likely to be unsuitable for further refined correlations.

### 1.7.2 The annualized relapse rate

The annualized relapse rate (ARR) is probably the most used outcome measure in MS drug clinical trials. The number of clinical relapses is supposed to be representative of

the disease's inflammatory component activity. A major problem with its interpretation is the variable definition used to define a relapse. Usually it is defined as patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating lesion within the CNS, current or historical, with a duration of at least 24 hours, in the absence of fever or infection (13). It should ideally be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic of MS for which no objective neurological findings are documented can provide reasonable evidence of a prior demyelinating event. However, pwMS might sometimes experiment other neurological symptoms (paroxysmal symptoms, Uthoff phenomenon, typically occurring several times in less than 24 hours) that may closely mimic true relapses. Hence, some authors consider new neurological symptoms as significant only if there is an associated change in the EDSS, the value of which being variable between studies, and other only consider this significant if the event justified treatment administration (i.e. steroids). In a population of "normally" active pwMS, the ARR usually ranges between 0.5 and 1.5.

### 1.7.3 The EDSS

Because the ARR mainly represents what is considered to be the inflammatory component of MS, but neither its progressive degenerative part nor the long term impact of relapses, it became usual to use a measure of « disability progression » along to the rate of relapses. Disability progression is defined as a sustained negative change (usually 3 months) in a chosen disability scale. Since 1983, the EDSS (see Supplementary material), designed in 1955 by John F. Kurtzke, is considered as the standard measure of disability (70). It is an ordinal scale rated from 0 (no neurological signs or symptoms) to 10 (death attributed to MS) with 0.5 intervals, calculated from 8 subscores related the important neurological spheres (visual, brainstem, pyramidal, cerebellar, sensitive, bowel and bladder, cerebral/cognitive, ambulation) derived from the neurological examination. In the lower part of the scale (from 0 to 3.5), the subscores are combined to produce the global score. In the middle part of the scale (from 4.0 to 5.5), the rating relies solely on the maximum unaided reported walking distance (i.e. 500 m for 4.0, 300 m for 4.5, 200 m for 5.0 and 100 m for 5.5), regardless of the type of underlying neurological alterations (provided it is sufficient to exceed 3.5). From 6.0 to 7.5, it is both the walking distance and the nature of support needed to ambulate that matters,

and in the higher part of the scale (above 8.0), only the global mobility and « general state » of the person is taken into account (amount of time of the day spent in bed, capacity to communicate and eat, effective use of arms). Despite a myriad of criticisms (71-75) regarding its standardization, sensitivity, responsiveness, intra- and inter-rater reliability – in brief, most of its psychometric properties – the EDSS continues to be the most widely accepted global measure of neurological function in MS. We consider this habit as probably responsible of several biases in practices and observations in the field of MS clinical practice and research, such as inappropriate group allocation and lack of significant effect detection in drug trials (especially for the progressive stages of the disease) (76), poor radio-clinical correlations even when specific MRI sequences are used (77), poor correlations between clinical scales and PRO measures, diagnostic errors or delays for patient with « transitional MS » who enter the progressive stage of the disease and imprecision in natural history studies. The major counter-argument against this criticism is of course that after Kurtzke's brilliant work, no new clinical scale was ever able to provide a better global quantification of the neurological status of pwMS.

## 1.7.4 The Multiple Sclerosis Functional Composite score

In 1994, at the beginning of the era of first large randomized placebo-controlled trials for potential drug therapies in MS, anticipating the need for more sensitive measures (e.g. for future trials where active comparators would be used instead of placebo), the US National MS Society sponsored a workshop of experts in order to evaluate which of the various available clinical outcome measures would be capable to overcome the above mentioned limitations of the EDSS for the evaluation of disability (78). The recommendations were focused on the creation of a new scale including multiple functional dimensions independent from each other and clinically relevant. The experts proposed the creation of the Multiple Sclerosis Functional Composite score (MSFC), obtained from the combination of 3 functional tests considered to be highly relevant regarding to MS manifestations, that is (i) the Timed 25-Foot Walk Test (T25FW) for the evaluation of ambulatory function (see 3.8.1), (ii) the 9-hole peg test (9HPT) for the evaluation of the upper limb function and (iii) the Paced Auditory Serial Addition Test (PASAT), as a surrogate marker of cognitive function. The results of these tests, for a group of pwMS, are combined into a z-score (which is calculated from the difference

obtained from the comparison of the 3 tests with the results of a chosen reference population) provide the value of the MSFC, which was shown to be easy to administrate, valid, reliable and responsive to change (79, 80), when compared to the EDSS. However, the MSFC has been criticized for its lack of clinical relevance in the routine clinical practice (especially when used as a global z-score), for the marked practice effect observed over the first administrations (80) of each test – particularly the PASAT –, for the absence of visual function component – because no valid and easily accessible clinical scale or test was available for this neurological sphere in MS at the time of the consensus meeting –, for the overall poor validity of the PASAT, and for its variable results as a function of the chosen reference population.

## 1.8 Walking disorders as outcome measures for MS

### 1.8.1 The Timed 25-Foot Walk Test: Pros and Cons

The introduction of the MSFC as an outcome measure for randomized clinical trials led to the diffusion of a short distance-based walk test to evaluate gait and lower extremity function, namely the Timed-25 Foot Walk (T25FW) (78, 80). According to the MSFC guidelines (81):

*« It is the first component of the MSFC administered at each visit. Patients may use assistive devices when doing this task. In clinical trials, it is recommended that the treating neurologist select the appropriate assistive device for each subject – generally the custom assistive device of the subject. The subject should be directed to one end of a clearly marked 25-foot course (clearly defined on the floor or on the wall) and instructed to stand just behind the starting line. The rater points out where the 25-foot course ends, then instruct the patient as follows: "I'd like you to walk 25 feet as quickly as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go". The rater must try to begin timing when the lead foot is lifted and crosses the starting line. The examiner should walk along with the patient as he/she completes the task. The rater must try to stop timing when the lead foot crosses the finish line. The examiner should then record the subject's walk time to within 0.1 second, rounding as needed. Round up to the next tenth if hundredth's place is > = .05, round down if hundredth's place is <.05 (e.g., 32.45" would round to 32.5" but 32.44" would round to 32.4"). The task is immediately administered again by having the patient walk back the same distance. »*

Hence, the descriptor of gait measured by the T25FW is walking speed (WS). While among other walking tests the T25FW has been considered as sufficiently valid, responsive to change and easy to administer, some authors have also argued that the T25FW could display variable results (80, 82) especially in more disabled pwMS with

slower WS. This has been attributed to practice effect, test-related fatigue, and motivational issues (83). In addition, the T25FW has been described by others as hampered by low responsiveness with marked floor and ceiling effects (84). This test-related variability of WS both in healthy subjects and pwMS led to the general acceptance that a change of at least 20% of WS measured by the T25FW had to be observed to consider as clinically significant (85, 86).

## 1.8.2 What does Walking Speed represent?

Walking speed obtained with the T25FW is thus considered as the most important descriptor of gait in MS. It should first be noted that in the context of other diseases and tests, WS has been measured according numerous other methodologies with static or dynamic starts (87), over distances ranging from 4 m (88) to undefined (89), according to type of walk instructed as « comfortable » (88, 89) or « as fast as possible » (90) paces, and measured with various devices, mainly stopwatches or accelerometers, or even sometimes questionnaires (91). Few head-to-head comparisons between those methodologies are available (92).

Besides these strictly methodological issues, one also needs to question what WS really represents relatively to gait function. There is a wealth of literature supporting the view that WS is the most important gait descriptor when quantifying gait performances. From a very pragmatic and functional point of view, it might seem obvious that a person who can walk fast probably has a « normal gait ». As a matter of fact, it has been shown that WS decreased with age in healthy subjects (89) and that a higher WS was associated with better outcomes such as survival in older adults (88), activities of daily living (91), long term physical impact of the disease in progressive forms of MS (90), and energy cost of walking (93) in pwMS. Despite these global correlations, WS provides no real qualitative information, especially concerning the underlying walking disorder. In the context of MS, spasticity, locomotor fatigability, incoordination, lower limb weakness, balance deficits may all contribute to WS decrease, but the sole T25FW does not display a good differential sensitivity to these. Finally, one may also postulate that different WS obtained from different methods may bring complementary rather than contradictory informations.

# 2  Objectives

The objectives of our work were:

(i)  To define and evaluate potential regulators of WS in MS (as measured by the T25FW), study their differential effect in pwMS with different disability status and healthy subjects, and hypothesize pathophysiological mechanisms underlying the observed differences:

   a. The chosen walking distance. We hypothesized that longer distance walking tests would yield lower WS and thus insights into potential pathological deceleration and fatigue related to MS. Two longer distances were evaluated: 100 and 500 m.

   b. The chosen type of walk instructed. We considered that « as fast as possible » instruction would yield a higher WS then the « comfortable pace », but we hypothesized that the relative difference in the obtained WS would be different between healthy volunteers and pwMS and might also be influenced by the degree of pwMS disability.

   c. The static versus dynamic start. Considering a higher WS would be obtained with a dynamic start by removing the acceleration phase of the walking evaluation, we hypothesized a difference in the acceleration capacity of pwMS and healthy volunteers might be demonstrated.

   d. The type of recording device. We postulated a human rater would produce more recording errors than an automated system and we wanted to measure the extent of these errors.

(ii)  To search for other dimensions than WS that may participate significantly to gait variance in a population of pwMS and healthy subjects. As a first step, in this Thesis will be described:

   a. The creation and validation of a new gait analysis system

   b. The determination of other dimensions than WS and their comparison between healthy volunteers and pwMS at different level of disability

# 3    Part I: Impact of confounding factors on the standardized evaluation of walking speed in multiple sclerosis

## 3.1  Evaluation of walking speed on a distance of 100 m - Comparison between the Timed 100-Meter Walk and the Timed 25-Foot Walk in multiple sclerosis

**Publication #1:** Phan-Ba R, Pace A, Calay P, Grodent P, Douchamps F, Hyde R, Hotermans C, Delvaux V, Hansen I, Moonen G, Belachew S. Comparison of the timed 25-foot and the 100-meter walk as performance measures in multiple sclerosis. *Neurorehabil Neural Repair.* 2011;25(7):672-9.

### 3.1.1  Introduction and objectives

As a first experiment to address the influence of walking distance on WS as measured by a short distance walking test such as the T25FW, we decided to study ambulation characteristics of pwMS on a longer distance, hypothesizing it would be lower, and perhaps more representative of their real walking capacities. We thus designed and evaluated the Timed 100-Meter Walk Test (T100MW). The 100-, 200-, 300-, and 500-m distances represent the ambulation range of EDSS scores of 5.5, 5.0, 4.5, and 4.0, respectively. We chose the 100 m distance, because it is the threshold in the EDSS beyond which pwMS require at least unilateral assistance. Our first objective was to compare WS of pwMS and healthy volunteers on the T25FW to the T100MW. We additionally wanted to evaluate the ability of these tests to predict walking limitations in ambulatory pwMS. In this context, we considered the EDSS threshold of 500 m as too low and proposed to regard pwMS with maximum reported walking distance (MrWD) of 4000 or 2000 m as already abnormal.  The threshold of 4000 m was chosen according to previous findings demonstrating that the maximum objective walking distance measured with an odometer in an ambulatory pwMS population was up to 4550 m (94).

### 3.1.2 Methods

#### 3.1.2.1 Population

A total of 141 persons with a diagnosis of relapsing or progressive MS (either primary or secondary) according to the Poser (12) and McDonald 2005 (95) criteria and 104 age- and sex-matched healthy volunteers used as a control group were enrolled in the study. The Ethics Committee of the CHU of Liege approved the study and written informed consent was obtained from all healthy subjects. No informed consent was needed from pwMS since this was part of their routine clinical evaluation.

#### 3.1.2.2 Data acquisition

Both pwMS and controls performed the T25FW and the T100MW. All the assessments were made by a certified MS nurse or by a physical therapist in charge of pwMS' rehabilitation programs. A certified EDSS rater collected all EDSS scores.

The MrWD was evaluated as follows: healthy volunteers all reported an MrWD superior to 4000 m, which was considered as "unlimited". pwMS were asked whether they had the feeling that during the past 4 weeks their average walking performance had been unlimited and whether they thought they could walk for more than 4000 m without aid or rest. If so, they were considered to have an "unlimited" MrWD. pwMS considering themselves unable to walk more than 4000 m were defined as having a "limited" ambulation and were asked to evaluate as accurately as possible their MrWD, that is, the maximum distance they thought they could walk without aid or rest, with a high risk of falling if they went on for a few meters more. pwMS who evaluated their MrWD as being less than 2000 m were considered to be pwMS with a so-called "restricted" ambulation. According to the EDSS guidelines, the accurate walking distance was measured for pwMS reporting a MrWD below 500 m.

The T25FW was performed according to the published standardized instructions (80).

For the T100MW, a 100 m walk was accurately measured in a corridor of at least 3 m width, devoid of obstacles. Running was prohibited. pwMS could use assistive devices if absolutely necessary to perform the test. Ankle–foot orthosis were permitted if worn from onset for all evaluations throughout the trial. The subject was directed to the end of a clearly marked 100 m course (defined on the floor) and instructed to stand just behind the starting line. We pointed out where the 100 m course ended and then instructed the patient as follows: "I'd like you to walk this 100 meter distance as quickly

as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go." Timing started when the lead foot crossed the starting line. The examiner could not walk along with the patient as she/he completed the task. Timing was stopped when the lead foot crossed the finish line. The examiner then recorded the subject's walking time to within .1 second, rounding up or down as necessary. We rounded up to the next tenth if the hundredth of a second's place was ≥0.05, rounded down if the hundredth of a second's place was <.05 (e.g., 55.45'' would round up to 55.5'' but 55.44'' would round down to 55.4''). On the day of the clinical evaluations, rehabilitation sessions or other demanding physical activities did not take place prior to the testing. The 2 sessions of the T25FW were always performed prior to the T100MW. Healthy volunteers performed the T25FW and the T100MW twice to establish the test–retest intraclass correlation coefficient (ICC).

To evaluate the inter-rater reliability of the tests, 50 healthy volunteers and 40 pwMS underwent a second evaluation for the T100MW and the T25FW by another rater after a 15-minute resting time.

The mean WS expressed in meters per second for both tests were calculated by dividing 100 m by the time to perform the T100MW and 7.62 m by the time to perform the T25FW.

### 3.1.2.3 Statistical analysis

A Wilcoxon rank sum test was performed to compare walking test scores in healthy controls and pwMS. Test–retest and inter-rater reliabilities were evaluated using ICC (96). The coefficient of variation (standard deviation divided by mean, expressed as a percentage) was used to compare relative variation between the 2 walking tests overall, by limited/restricted ambulation, and within each step of EDSS. The results from the 2 methods were also compared in accordance with the principles described by Altman and Bland (97). Spearman rank analyses were used to assess the strength of the correlation between the T25FW, the T100MW, the EDSS, and the MrWD, and the coefficient of determination was obtained from a linear regression excluding outliers. The area under the receiver operator characteristic (ROC) curve provided an overall measure of the accuracy of each walking test in predicting limited ambulation. Last, a *t*-test was used for between groups comparisons, whereas a paired *t*-test was used for

within group comparisons of the mean WS on the T100MW with the mean WS on the T25FW.

All statistical tests were applied with a 2-tailed analysis and .05 as a level of significance.

### 3.1.3 Results

A total of 141 pwMS with a mean age of 40.0 ± 12.4 years and an EDSS score ranging from 0 to 5.5 (median = 2.5) and 104 healthy volunteers with a mean age of 35.4 ± 13.0 years participated in the study (Table I). We observed that 53 out of the 141 (37.6%) pwMS had a "limited" ambulation defined by an MrWD ≤ 4000 m. Forty-four subjects (31.2%) had a so-called restricted ambulation, defined by an MrWD ≤ 2000 m. The subgroup of pwMS who underwent a second analysis for the inter-rater ICC calculation and the whole pwMS population had comparable baseline characteristics, as well as subgroups stratified according to their EDSS as mild (0-2.0, n = 63), moderate (2.5-3.5, n = 38) or high (4.0-5.5, n = 40) (data not shown).

**Table I:** Characteristics of pwMS and control subjects

|  | pwMS | Healthy Controls |
| --- | --- | --- |
| Number of pwMS/controls | 141 | 104 |
| Gender (% female) | 68.8 | 63.5 |
| Age (mean ± SD, range) | 40.0 ± 12,4, 14-74 | 35.4 ± 13.0, 18-60 |
| EDSS (median, range) | 2.5, 0-5.5 | |
| MS type (%, RR/PP) | 90,3/9,7 | |
| pwMS with limited ambulation[1] | | |
|     Number (%) | 53 (37.6) | |
|     MWD in metres[2] (median, range) | 800, 100-4000 | |
| pwMS with restricted ambulation[3] | | |
|     Number (%) | 44 (31.2) | |
|     MWD in metres (median, range) | 600, 100-4000 | |

RR: Relapsing-Remitting; PP: Primary Progressive; 1. Limited ambulation was defined as the inability to walk more than 4000 m;  2. MWD: Maximum Walking Distance; 3. Restricted ambulation was defined as inability to walk more 2000 m

In the pwMS population, the time taken to perform the T100MW ranged from 30.6 to 197.9 s, with a median of 53.9 s, compared with a range of 33.1 to 62.1 s in healthy

volunteers with a median of 46.1 s (Table II). The T25FW was performed in a time ranging from 2.9 to 20.7 s (median = 4.4 s) in pwMS and from 2.8 to 5.2 s (median = 3.7 s) in healthy volunteers. Timed performances in both tests were significantly weaker for pwMS when compared with that of healthy volunteers (both p<0.0001). In every subpopulation of pwMS with EDSS scores ranging from 0 to 2.0, 2.5 to 3.5 and 4.0 to 5.5, both tests were also significantly altered when compared with healthy volunteers (p=0.018, p<0.0001, and p<0.0001, respectively).

**Table II:** Time values (s, median, range) for the T100MW and the T25FW in different

| population subsets | T100MW | T25FW |
|---|---|---|
| All pwMS (n=141) | 53.9 (30.6 - 197.9) | 4.4 (2.9 - 20.7) |
| pwMS, EDSS 0-2.0 (n=63) | 49.3 (30.6 - 64.3) | 3.9 (2.9 - 5.4) |
| pwMS, EDSS 2.5-3.5 (n=38) | 56.5 (44.7 - 88.0) | 4.5 (3.3 - 7.7) |
| pwMS, EDSS 4.0-5.5 (n=40) | 78.0 (43.0 - 197.9) | 5.81 (4.0 - 20.7) |
| Healthy control volunteers (n=104) | 46.1 (33.1 - 62.1) | 3.7 (2.8 - 5.2) |

T100MW: Timed 100-Metre Walk Test; T25FW: Timed 25-Foot Walk Test.

In healthy volunteers (n=104), the test–retest ICC was slightly better for the T100MW (0.930) than for the T25FW (0.880). To compare the inter-rater reliability of both tests, a subgroup of 50 controls and 40 pwMS underwent a second testing by a different rater, and the inter-rater ICC was calculated. The inter-rater ICC of the T100MW and T25FW were not significantly different between healthy volunteers (0.886 vs. 0.884, respectively) and pwMS (0.953 vs. 0.942, respectively).

The coefficient of variation (CV) was calculated to measure the dispersion of results obtained by both tests. Overall, the T100MW demonstrated less variability with a CV of 41% when compared with a CV of 45% for the T25FW. In pwMS with limited ambulation, the CVs for the T100MW and T25FW were 41% and 46%, respectively. The same was true for pwMS with restricted ambulation (T100MW CV = 40% vs. T25FW CV = 46%). On examination of CVs by EDSS score, differences between the 2 walking tests were observed among pwMS with mid-range EDSS scores (2.5-3.5). The T100MW displayed less relative variability in this range of EDSS than the T25FW, with CVs

ranging from 5% to 18% for the T100MW (Figure 1A) and from 14% to 25% for the T25FW (Figure 1B). It is important to emphasize that in this particular mid-range EDSS interval from 2.5 to 3.5, considered by definition to be fully ambulatory according to EDSS rules, 42.1% (16/38) of pwMS had a limited ambulation and 26.3% (10/38) had a restricted ambulation according to our aforementioned criteria.

Bland and Altman (BA) plots with limits of agreement were calculated to assess test–retest and inter–rater agreements. Between test and retest, the BA plots showed an



**Figure 1.** Coefficient of variation (CV, standard deviation divided by mean, expressed as a percentage) showing the distribution of the T100MW (A) and the T25FW (B) values by EDSS step, demonstrating less relative variability for the T100MW in the mid-range EDSS steps (2.5-3.5). Bland and Altman plots showing similar agreement across test and retest between the T100MW (C) and the T25FW (D). Equivalent agreements for the T100MW (E) and the T25FW (F) were also observed between raters. Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 25-Foot Walk Test; EDSS, Expanded Disability Status Scale.

equally good agreement for each of the walking tests (Figure 1C and D), with a similar

number of pwMS beyond the limits of agreement. Between the raters, mean differences were also near 0 for both tests, with nearly all points falling within the limits of agreement (Figure 1E and F).

Spearman rank correlations (Table III) showed that the T100MW and the T25FW correlated equally well with the EDSS, with *r-values* of 0.67 (p<0.0001) and 0.67 (p<0.0001), respectively. The overall correlation between the 2 tests was excellent (*r*=0.92, p<0.0001). In pwMS with "limited" or "restricted" ambulation range for whom the MrWD could be approximated, the T100MW correlated better with estimated MrWD than the T25FW (*r*=−0.79 vs. *r*=−0.71 in the "limited" ambulation population and *r*=−0.77 vs. *r*=−0.69 in the "restricted" ambulation population).

**Table III:** Spearman rank correlations between walking tests, EDSS and walking distance in different pwMS population subsets

| Correlation* | Number of pwMS | Spearman Rank |
|---|---|---|
| T25FW and EDSS | 141 | 0.6686 |
| T100MW and EDSS | 141 | 0.6740 |
| T25FW and T100MW | 141 | 0.9227 |
| pwMS with limited ambulation | | |
| T25FW and walking distance | 53 | -0.7121 |
| T100MW and walking distance | 53 | -0.7916 |
| pwMS with restricted ambulation | | |
| T25FW and walking distance | 44 | -0.6861 |
| T100MW and walking distance | 44 | -0.7738 |

T25FW: Timed 25 Foot Walk Test; T100MW: Timed 100 Meter Walk Test; 1. Limited ambulation was defined as the inability to walk more than 4000m; 2. Restricted ambulation was defined as the inability to walk more than 2000m ; *: All p-values were < 0,0001

We also calculated the coefficient of determination ($R^2$) to estimate the proportion of variation in MrWD explained by the walking tests in pwMS with "restricted" ambulation. The variation in MrWD was explained for 44.1% with the T100MW (Figure 2A) versus 29.6% for the T25FW (Figure 2B). The area under the ROC curve (AUC) was estimated to compare the trade-off between sensitivity and specificity and the value of both tests in predicting limited ambulation (Figure 2C). We did not find a meaningful difference between the AUC of the T100MW (0.884) and the T25FW (0.881) in the overall

population.



**Figure 2.** Correlation between the T100MW (A) and the T25FW (B) values and the maximum walking distance (MWD) and corresponding coefficient of determination ($R^2$). Receiver operator characteristic curve analysis of the T100MW (black line) and the T25FW (dashed grey line) and corresponding area under the curve (AUC) values (C). Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 100-Foot Walk Test.

Finally, the mean WS derived from the T100MW and the T25FW was significantly lower (both $p<0.0001$) in pwMS (1.8 ± 0.5 and 1.7 ± 0.4 m/s, mean ± SD, respectively) compared with healthy volunteers (2.2 ± 0.3 and 2.1 ± 0.3 m/s, mean ± SD, respectively). The evaluation of ambulation impairment through the calculated mean WS confirmed that performances were significantly altered for the 2 tests (T25FW and T100MW) in the global pwMS population compared with healthy volunteers and in subsets of pwMS either with high (4.5-5.5) or low (0-3.5) levels of EDSS status (Figure 3A). Furthermore, we paradoxically observed in individual performances that the T100MW mean WS was very frequently faster than the T25FW mean WS, both in healthy volunteers (data not shown) and in the pwMS population, as displayed by a positive absolute difference between both tests in a majority of pwMS (109/141 pwMS, 77.3% of the pwMS population, Figure 3B). In agreement with this finding, the T100MW mean WS was found to be significantly higher than the T25FW mean WS, both in healthy controls and in each subgroup of pwMS, defined by an EDSS ≤ 3.5 or ≥ 4.0 ($p<0.0001$, $p<0.0001$, and $p=0.009$, respectively; Figure 3A). Consistently, in healthy volunteers as well as in different subsets of pwMS, the mean WS over a 100 m distance was paradoxically ~7% higher than the MWS over 25 feet, as demonstrated by the mean values of the ratio between respective WS calculated for each tests in individual subjects (Figure 3C).

### 3.1.4 Discussion

In the present study, we revealed minor differences modestly favouring the use of the T100MW over the T25FW for the evaluation of WS in persons with MS. We also paradoxically observed a higher mean WS when measured with the T100MW compared

to the T25FW, both in healthy subjects and in distinct subsets of our pwMS population.

The variability of the WS calculated from the T25FW is related to different factors, including the level of accelerating capacity during the very first meters of the test. As a matter of fact, it can take half of the test for many pwMS to reach their maximum WS on a 25-foot-long distance, since the patient is asked to begin just behind the starting line. This is probably in line with the finding of a higher mean WS calculated on 100 m (T100MW) compared with the 25-foot distance (T25FW), while we had actually hypothesized that the longer the distance, the lower the WS would be because of motor fatigue. One can assume that the fluctuant phase of acceleration in the first steps of the T25FW makes it a poor indicator of the real maximum WS over a short distance. Hence, variations in the T25FW duration are not solely representative of maximum WS differences.

The slightly better reliability and lower variability of the WS obtained from the T100MW indicate that other confounding factors may have less influence on a walking test based on a longer distance. In this regard, additional studies investigating the impact of static vs. a dynamic start, the instructed type of walk and the precision of time recording are warranted.

The T100MW appeared to be better correlated with the ambulation range (MrWD) than the T25FW in pwMS with "limited" (MrWD ≤ 4000 m) or "restricted" (MrWD ≤ 2000 m) ambulation. This was also suggested by the coefficient of determination calculation results. It is important to emphasize that the MrWD was evaluated on a subjective basis between 500 and 4000 m, but pwMS' report of the MrWD remains the most widely used approach in trial guidelines and has been shown to be reasonably well correlated with values acquired from more sophisticated measures (94).
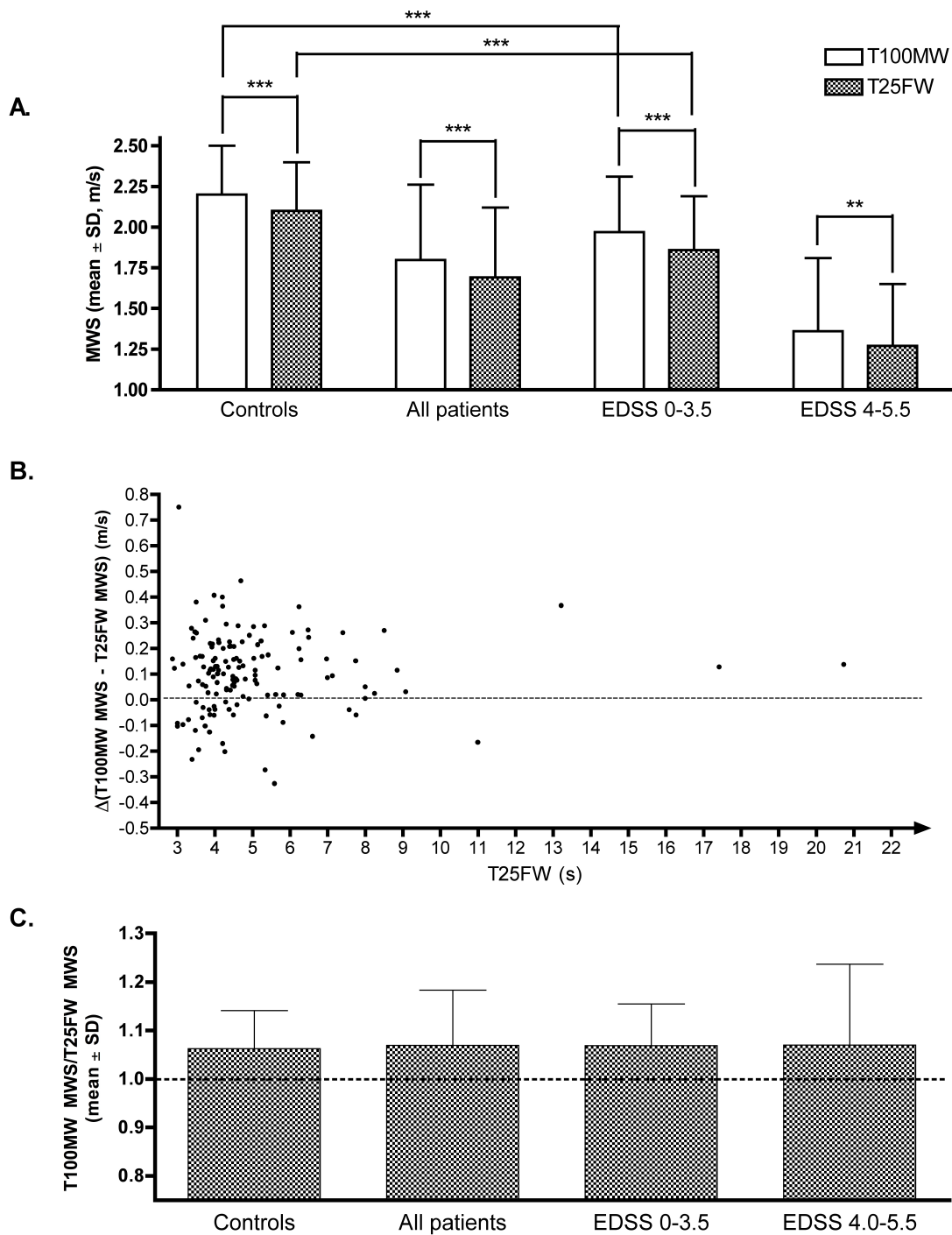
**Figure 3.** Mean walking speed (MWS) ± standard deviation assessed by the T100MW and the T25FW in healthy control volunteers, in all pwMS and in different subsets of EDSS range in the MS population (A); ***$p < .0001$; **$p = .009$; Note that all $p$ values were <.0001 for all respective comparisons of the 2 tests between pwMS and controls but only significant differences between controls and the low EDSS score group were highlighted. Absolute differences between the T100MW and the T25FW MWS in individual pwMS were expressed as a function of T25FW performances (B). Mean ± standard deviation of T100MW MWS/T25FW MWS speed ratio values in healthy control volunteers, in all pwMS and in different subsets of EDSS scores (C). Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 25-Foot Walk Test; EDSS, Expanded Disability Status Scale.

When performing and comparing several types of gait evaluations, the order of assessment also has to be taken into account. In our study, one may argue that we did

not assess the possible effect of the T25FW over the T100MW. However, the T25FW was always performed first. We postulated that the influence of a previous 7.62 m distance performed twice should only be of minor importance over the next 100 m WS performed after a 5-minute stop in between.

Beyond the attempts to develop new walking tests more predictive of the accurate MrWD and maximum WS, there is a need for research efforts to gain more insight into the integrated comprehension of each individual tests with respect to the multiple identified parameters affecting the quality of ambulation, whether related to MS or not. Although diffuse cerebral white matter dysfunction may play a role in early walking disability, the main pathological substratum of gait dysfunction below an EDSS of 4.0 is likely to reflect mostly spinal cord demyelination and acute relapse–induced and/or chronic relapse–independent axonal loss or dysfunction, especially at the level of the pyramidal tracts (98). In our study, the T25FW and the T100MW as well as the corresponding WS displayed abnormal values in the low levels and mid-range EDSS values (EDSS ≤ 3.5), providing evidence of ambulation limitations at early stages of MS evolution. Such early walking limitations are not directly translated in the EDSS status calculation before the 4.0 milestone. The early insidious progression or relapse- driven accumulation of gait disability heavily contributes to the genesis of MS-related motor fatigue and its detection might be a guiding tool for assessing early specific therapeutic interventions. Moreover, in early stages of MS, any increase in the stringency of our analyses of walking performances may allow us to better delineate the spectrum of clinical improvement under highly active disease-modifying treatments (99).

To evaluate locomotor fatigability and limitations of MrWD, others have proposed to measure the maximum walked distance during time-based evaluations (92, 100). We consider that distance-based evaluations (such as 100-m or 500-m walking tests) may be more suitable than time-based evaluations (such as 2-, 3-, or 6-minute walking tests) for 2 reasons: (i) walking tests over a defined distance may allow pwMS to better dose their effort since they start with a concrete visuospatial representation of the length of the test and (ii) in duration-based walking tests, the rater has to ask the patient to walk "as fast and as far as he/she can" over a defined time, which may be a confusing dual task in comparison to the more straightforward recommendation to walk "as fast as he/she can" in distance-based evaluations. Our hypothesis that WS would be lower over a distance of 100 m compared to 7.62 m was not confirmed, indicating that longer

distances might be necessary to capture pathological motor fatigue (see 5.5).

Altogether, we consider that the integration of multiple modalities of ambulation tests to develop composite walking indices that could be highly sensitive to change to better capture the efficacy of therapeutic interventions, especially in primary and secondary progressive forms of MS, is a promising approach.

## 3.2 Evaluation of the acceleration capacity of pwMS and its influence on WS measured over a short distance

**Publication #2:** Phan-Ba R, Calay P, Grodent P, Delrue G, Lommers E, Delvaux V, Moonen G, Nagels G, Belachew S. A corrected version of the Timed-25 Foot Walk Test with a dynamic start to capture the maximum ambulation speed in multiple sclerosis patients. *NeuroRehabilitation.* 2012; 30(4): 261-6.

### 3.2.1 Introduction

Among the several hypotheses proposed to influence the WS achieved over a short distance and which might explain the discrepancy in WS values we observed when evaluating gait function according to the T25FW or the T100MW, we decided to test the influence of the starting mode. « Dynamic or static start » has already been regarded as one of the methodological factors responsible for poor comparability between studies (87, 101), but no head-to-head comparison has ever been performed among the various methodologies previously used to assess the WS in MS. Based on works demonstrating minimal alterations in balance and postural transition parameters (102) in pwMS, even with minimal disability (103), we also speculated that the relative duration and length of the accelerating phase during the very first meters of the test could contribute to the slower WS observed on a short distance walking test.

In order to investigate the potential weight of these first meters of acceleration in the T25FW performances, we proposed a corrected version of the test where a dynamic start is allowed 3 meters before the starting line (i.e. T25FW+). We assumed that 3 meters, which represent nearly 40% of the full 25-foot distance was likely enough to reach a maximum WS for most pwMS. Hence, this paradigm allows to exclude or at least significantly reduce the relative impact of the "acceleration phase" in the test and to compare the observed mean WS on the same distance with that of the conventional T25FW (i.e. with a static start right behind the line).

### 3.2.2  Methods

#### 3.2.2.1  Population studied

Sixty-four relapsing or progressive pwMS diagnosed according to the McDonald 2005 criteria (95) and 30 age and sex matched healthy controls used as a control group were selected for this cross-sectional study. We accepted pwMS with a broad range of walking performances with an EDSS ≤ 6.5.

The ethics committee of the faculty of medicine of the university of Liège approved the study protocol.

#### 3.2.2.2  Walk Test paradigm

The T25FW was performed according to the published standardized instructions (80).

The T25FW+ was also strictly following the guidelines of the T25FW, except that the subjects were allowed to take a 3 meters run-up before the starting line. This run-up was clearly demarcated on the ground. The raters were instructed for both tests to start the stopwatch as soon as the lead foot crossed the starting line of the 25-foot distance, and to stop it when the lead foot crossed the finish line.

The raters had been trained and certified for the administration of all the tests from the MSFC score and EDSS scores were collected by certified EDSS-raters.

The T25FW and the T25FW+ were performed as the first part of a multi-test evaluation during routine clinical evaluations, in an outpatient neurological MS department, between November 2009 and October 2010. The T25FW was first performed twice as well as the T25FW+ after 5 minutes of break in between. For both tests, the results were expressed as the mean time of the 2 trials.

The mean WS expressed in meters per second for both tests were calculated by dividing 7.62m (i.e. 25 feet) by the time to perform the T25FW or the T25FW+.

#### 3.2.2.3  Statistical analysis

Non-parametric unpaired t-tests were used for between group comparisons, while non-parametric paired t-tests were used for within group comparisons. Pearson's correlation coefficient was used to assess the relationship between the two tests. All statistical tests were applied with a two-tailed analysis and 0.05 as a level of significance, and were performed using GraphPad Prism, version 4.0b for Macintosh, GraphPad Software, San Diego California USA (www.graphpad.com).

### 3.2.3 Results

The baseline characteristics of pwMS (n=64) and healthy volunteers (n=30) are summarized in Table IV. No major differences were observed between the two populations. In the pwMS population, the median EDSS was 3.0 (ranging from 0 to 6.5). The distribution of the population throughout the different EDSS subgroups was harmonious.

**Table IV:** Characteristics of pwMS and control subjects

|  | pwMS | Healthy Controls |
|---|---|---|
| Number of pwMS/controls | 64 | 30 |
| Gender (% female) | 59 | 71 |
| Age (median, range, years) | 39, 15-64 | 25, 18-60 |
| Body Mass Index (mean ± SD, kg/m$^2$) | 23.55 ± 4.2 | 25.18 ± 9.6 |
| EDSS (median, range) | 3.0, 0-6.5 | n.a. |
| EDSS 0-2.0 (number of patients, %) | 25 (39) | n.a. |
| EDSS 2.5-4.0 (number of patients, %) | 24 (37.5) | n.a. |
| EDSS 4.5-6.5 (number of patients, %) | 15 (23.4) | n.a. |
| MS type (CIS/RR/SP/PP, %)[1] | 9.4/65.6/12.5/12.5 | n.a. |
| Disease duration (mean ± SD, range, years) | 10.4 ± 9.3, 0-35 | n.a. |

1: CIS, Clinically Isolated Syndrome; RR, Relapsing-Remitting; SP, Secondary Progressive; PP, Primary Progressive.

The two tests correlated slightly better in pwMS (Pearson's correlation coefficient, r=0.9791, p<0.0001) than in healthy volunteers (r=0.8554, p<0.0001). As highlighted by individual absolute differences in time (Figure 4A) and in mean WS (Figure 4B), the majority of pwMS (92%, 59/64, Figure 4C) and healthy volunteers (80%, 24/30, Figure 4D) performed consistently faster on the T25FW$^+$ than on the T25FW with varying levels of differences between the two tests (Figure 4).
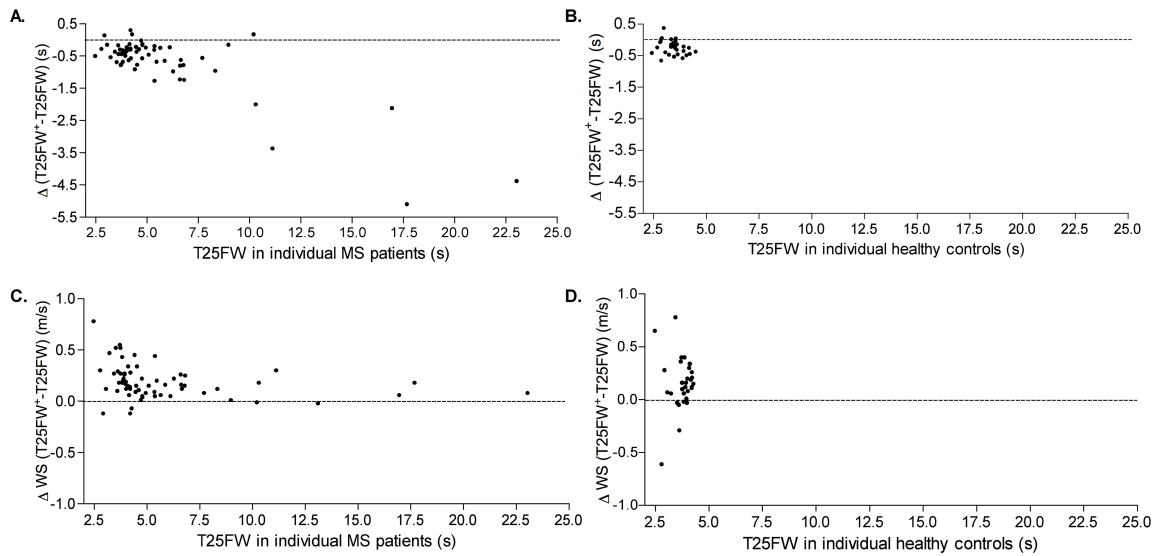
**Figure 4:** Absolute difference between the T25FW+ and the T25FW (ΔT25FW+-T25FW) in individual pwMS (A) and healthy controls (B). Absolute difference between the mean calculated walking speed (WS) in both tests (ΔWS (T25FW+-T25FW)) in pwMS (C) and healthy controls (D). All results were classified by increasing T25FW.

The difference between the two tests was further confirmed by a mean WS that was significantly higher for the T25FW+ compared to the T25FW in pwMS ($1.80 \pm 0.65$ vs $1.62 \pm 0.57$, respectively, mean $\pm$ SD, m/s, $p<0.0001$) and healthy controls ($2.46 \pm 0.43$ vs. $2.31 \pm 0.37$, respectively, mean $\pm$ SD, m/s, $p<0.0001$) (Figure 5A). Ambulation speed performances were also significantly slower for pwMS compared to that of healthy volunteers in both tests ($p<0.0001$ for both comparisons). The T25FW+ was performed consistently faster than the T25FW in all subgroups of pwMS stratified according to their EDSS status (0 to 2.0, 2.5 to 4.0, and 4.5 to 6.5; all $p<0.0001$, Figure 5B). In order to dichotomize pwMS according to their normal versus abnormal walking performances, we fixed a threshold value of 4.43 seconds, corresponding to the mean T25FW in healthy volunteers plus twice its standard deviation. We then separated the MS population between the so-called "normal walker" group with a T25FW≤4.43 s (n=31, 48% of the population) and the "slow walker" group with a T25FW>4.43 s (n=33, 52% of the population). The mean WS was also significantly faster in the T25FW+ both for the "normal" and "slow" walker MS groups ($p<0.0001$, Figure 5C). We calculated the individual relative differences between WS in the two tests: i.e. the difference between WS on T25FW+ minus WS on T25FW, divided by WS on T25FW+. The mean relative difference between WS in the two tests (ΔWS (T25FW+-T25FW)/WS T25FW+) was significantly higher in pwMS compared to healthy volunteers ($10.2 \pm 7.7\%$ versus $5.7 \pm$

9.1%, mean ± SD; p=0.0148, Figure 6A). No significant difference was found in the mean relative difference between WS of the two tests for the subgroups of pwMS at different levels of disability according to their EDSS status (Figure 6A).
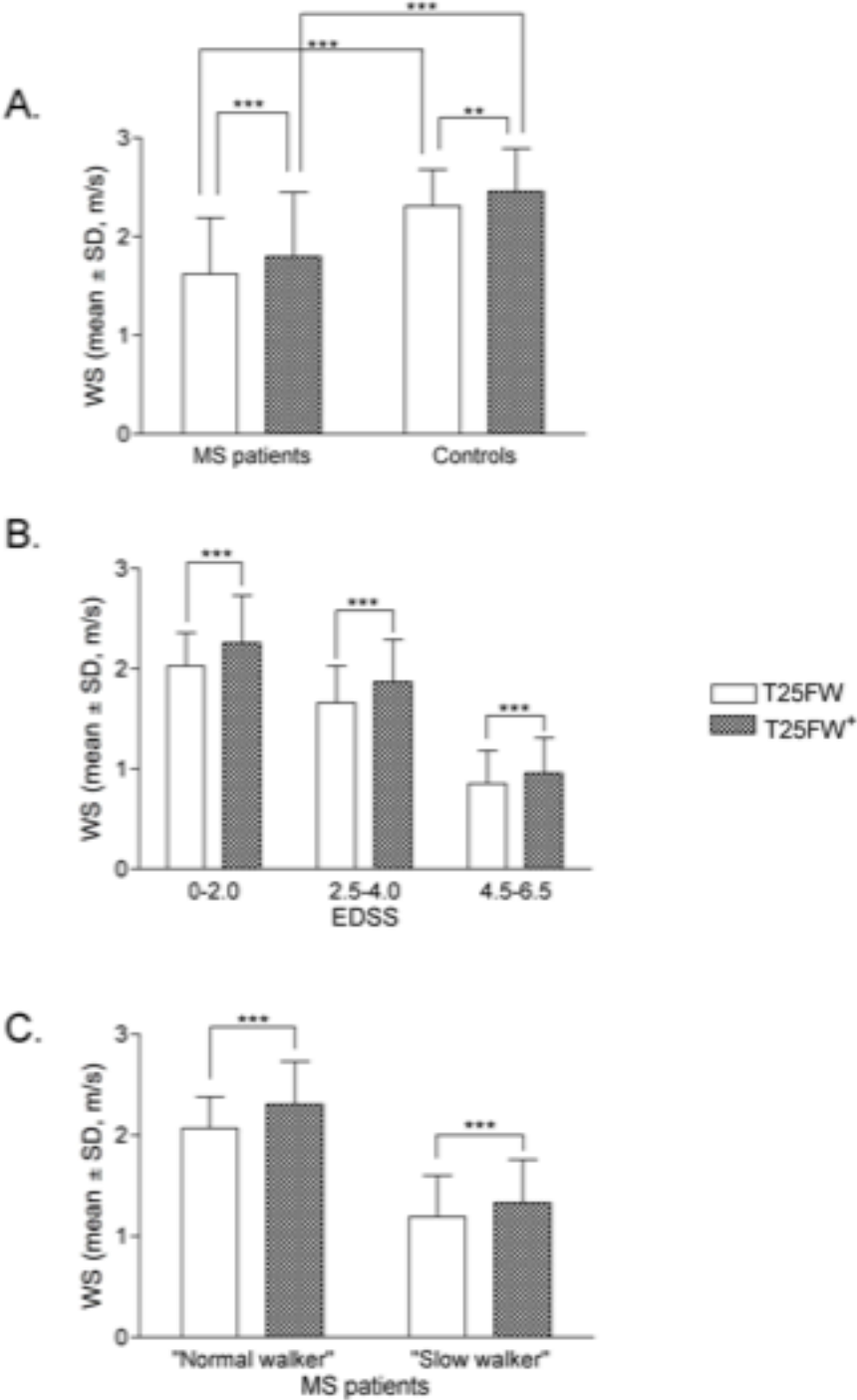


**Figure 5:** Histograms depicting the mean walking speed (WS) on the T25FW and the T25FW+ in the global pwMS population and healthy controls (A), across different levels of disability status evaluated through the EDSS (B) and in "normal" versus "slow" walkers.

The mean relative difference between WS in the two tests was also significantly higher in "normal" (10.0 ± 7.2%, mean ± SD, p=0.0461) and "slow" (10.4 ± 8.2%, mean ± SD, p=

0.0363) walker pwMS compared with that of healthy volunteers (5.7 ± 9.1%, mean ± SD) (Figure 6B). No significant difference was found in this regard between "normal" and "slow" walkers in the pwMS population (Figure 6B).
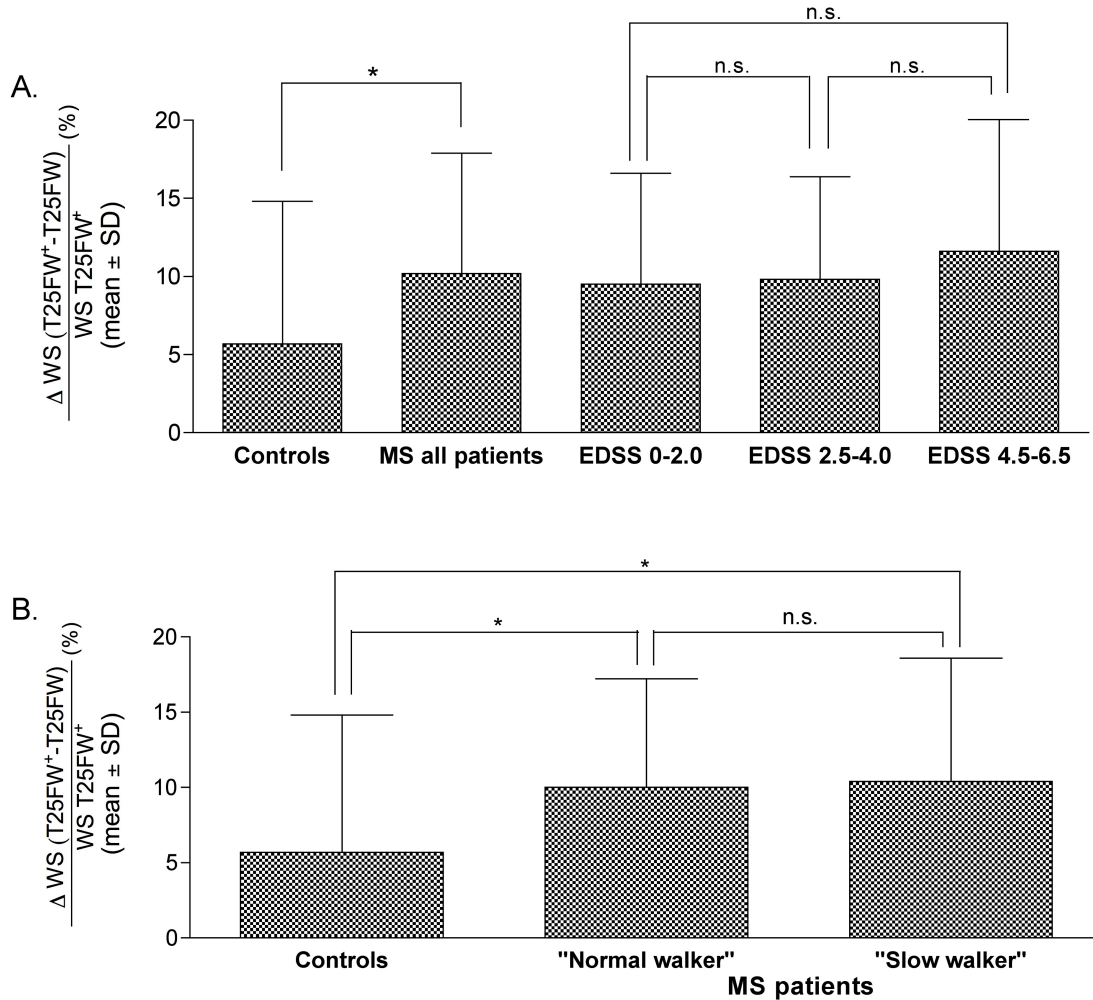


**Figure 6:** Histograms depicting the mean relative difference between WS on the T25FW$^+$ and T25FW ($\Delta$WS (T25FW$^+$-T25FW)/ T25FW$^+$) in healthy controls, the global MS patients population (A), across different levels of disability status evaluated through the EDSS (A), and in "normal" versus "slow" walking MS patients (B).

### 3.2.4 Discussion

The present study shows that the time to reach the maximum WS has a significant impact in the results of the conventional T25FW, since a run-up of 3 meters can lead to a significantly higher mean WS measured on the same 25 foot distance, both in healthy volunteers and in all subsets of pwMS. This observation is important since we show that the difference produced by the applied protocol (static vs. dynamic) can account for approximately 10% of the measured WS, that is half of what is considered to be a significant change in clinical practice and trials. Removing part if not all of this

accelerating phase to reach the maximum speed using a 3 meters run-up before the T25FW induced a more important difference between the two tests in pwMS compared to healthy volunteers, regardless of their EDSS status or their ambulation impairment. Indeed, the difference between the two tests was also significantly less pronounced in healthy volunteers than in the so-called "normal walker" pwMS, who had no ambulatory deficit according to their timed walk test results. This observation may either reflect the need for a longer distance of accelerating phase to reach the same maximum pace in pwMS, or an increased latency to start walking after the start signal. The first hypothesis has been validated previously (104), by demonstrating that pwMS took a longer time to initiate gait by adopting a different strategy than healthy volunteers. These authors concluded that those changes were part of a functional strategy adopted by pwMS aimed at walking more slowly in order to avoid falls. Even though this conclusion remains debatable, their results are in line with ours, and it can be concluded that pwMS consequently perform a shorter proportion of the classical T25FW at their maximum WS, indicating that the maximum WS per se and the capacity of pwMS to accelerate on a specific distance are clearly distinct outcome measures, which might be differently affected by symptoms, clinical course or therapies in MS. The second hypothesis – an increased latency – is likely to depend more on the motor reaction time to a simple command, which could for example be altered in the presence of a mild cognitive dysfunction. Several studies have demonstrated that true walking impairment or even simple postural control abnormalities can be seen in the early course of MS (102, 103, 105, 106) as well as in pwMS where the level of disability remain low or unapparent, with no clinically detectable signs of CNS lesions according to the Kurtzke functional system scores. Hence, beyond the typical pyramidal, proprioceptive, and cerebellar MS symptoms affecting ambulation, other factors that remain to be elucidated probably contribute to walking impairment in this disease. In this regard, the potential link between early cognitive impairment and gait disability should be further investigated (107). If our second hypothesis is true, the present data would strengthen the potential influence of attention network and information processing speed systems alteration - which is frequent early in MS (108, 109) - in gait and postural disturbances (105, 107). For clinical trials, particularly when addressing progressive forms of MS, as well as for the field of neurorehabilitation, these results emphasize that the classical T25FW needs to be revisited with a propelled start (T25FW+) if its objective remains to capture the

real maximum WS of pwMS on short distances. Then only, should the T25FW[+] performances be compared to WS measurements performed using longer distance tests such as the T100MW. This will allow the development of new insightful outcome measures through the calculation of ratios between WS measured on short and longer distances. We think such deceleration indices may be reliable indicators of locomotor fatigability, which might be present even at early stages of the disease course (110).

## 3.3 Influence of the type of walk on walking speed in multiple sclerosis

### 3.3.1 Introduction and objectives

Since the interference of the instruction given to the subject before the start signal appears as an obvious potential bias in the measures of any timed walked test, we retrospectively compared the results (in term of WS) obtained with the « as fast as possible » (AFAP) instruction over the T25FW[+], compared with those of the same test administered with the instruction to walk at a pace considered « comfortable » by the subject (preferred pace, PrP) in a population of pwMS and healthy volunteers.

We generally assume that the AFAP type of walk is representative of the « best » locomotor performances a subject can achieve, and hence of the integrity of his/her underlying « locomotor apparatus », i.e. the CNS and musculoskeletal systems joint functioning.

Alternatively however, the WS is also sometimes considered as a functional parameter (as in the MSFC or in the geriatric population), representative of the potential consequences of gait dysfunction on everyday life. One could argue then that the WS should be measured in the PrP type of walk, since most people usually do not walk as fast as they can in their normal daily environment.

Finally, studying the difference between PrP and AFAP WS may provide indirect insight into mechanisms regulating PrP WS (and their perturbation in MS), especially if we consider the AFAP WS as a more constant parameter.

The objectives of this work were thus (i) to study the relative difference between the PrP and AFAP measured WS in a cohort of pwMS and healthy volunteers and to study the influence of (ii) the PrP WS and (iii) the disability status as measured by the EDSS over this difference.

### 3.3.2 Methods

We retrospectively analysed WS from 58 pwMS and 39 healthy volunteers who performed several timed walk tests in the context of a study aimed at validating a new gait analysing system which will be described later in this work (see Part II).

The Ethics Committee of the CHU of Liege approved the study and written informed consent was obtained from all healthy subjects.

Start and stop instructions were given by the rater, but start and stop times were recorded by an automated system, with a spatio-temporal resolution of 1 cm and 15 Hz, respectively. Start and stop times were defined as the instant when the centre of the subject (i.e. the middle point between the subject's legs positions, see Part II) crossed the start or finish lines, respectively. Start and finish lines were clearly demarcated on the ground.

Subjects were asked to walk the T25FW$^+$ twice in the PrP type, with the instruction to walk « at their comfortable, usual pace », and then twice in the AFAP type, according to the same protocol as in (111).

WS were automatically generated and expressed in meter per second.

Non-parametric unpaired t-tests were used for between group comparisons, while non-parametric paired t-tests were used for within group comparisons. Pearson's correlation coefficient was used to assess the strength of observed relationships. All statistical tests were applied with a two-tailed analysis and 0.05 as a level of significance, and were performed using GraphPad Prism, version 4.0b for Macintosh, GraphPad Software, San Diego California USA (www.graphpad.com).

### 3.3.3 Results

Baseline characteristics of the two populations did not displayed marked differences (Table V), except for the age, which was higher in the pwMS group.

The pwMS population included subjects with a diagnosis of MS according to the 2010 McDonald criteria (13), a stable disease course with no relapses in the prior 3 months, with a median EDSS of 3.5 (range, 2-5.5), a mean disease duration of 11 year, and a disease type repartition of 20/52.7/10.9/16.4 (CIS/RR/SP/PP, %).

**Table V:** Characteristics of pwMS and healthy controls

|  | pwMS | Healthy Controls |
|---|---|---|
| Number | 55 | 37 |
| Gender (% female) | 45.9 | 60 |
| Age (median, range, years) | 42, 20-69 | 28, 22-63 |
| Body Mass Index (mean ± SD, kg/m$^2$) | 23.28 ± 4.61 | 23.97 ± 3.91 |
| EDSS (median, range) | 3.5, 2-5.5 | n.a. |
| MS type (CIS/RR/SP/PP, %)[1] | 20/52.7/10.9/16.4 | n.a. |
| Disease duration (mean ± SD, range, years) | 10.9 ± 10, 0-42 | n.a. |

1: CIS, Clinically Isolated Syndrome; RR, Relapsing-Remitting; SP, Secondary Progressive; PP, Primary Progressive.

The mean WS measured along 25 foot according to the AFAP instruction were comparable to previous results, with values of 1.67 ± 0.49 and 2.22 ± 0.3 (m/s, mean ± SD) for pwMS and healthy volunteers, respectively. pwMS walked significantly slower compared to control subjects in the AFAP type of walk (p<0.0001, Figure 7A). The WS measured in PrP was also significantly different between the 2 populations (p=0.0003), with values of 1.21 ± 0.33 and 1.43 ± 0.17 (m/s, mean ± SD), for pwMS and healthy volunteers, respectively (Figure 7A).

The relative difference between the AFAP WS and the PrP WS was significantly reduced in the pwMS subjects compared to healthy volunteers, with mean values of 26 ± 1.5 and 35 ± 1.3 (%, ± SD, p<0.0001), respectively (Figure 7B).

The WS measured in the AFAP type was found to be less strongly correlated to the WS measured in the PrP type in healthy volunteers (Figure 8A) than in pwMS (Figure 8B), with *r-values* of 0.51 vs. 0.87, respectively (both p<0.0001).

Finally, we assessed the correlation between the PrP WS and the relative difference between AFAP and PrP WS in the two populations. A significant negative correlation was found in the healthy volunteers population (*r*=-0.41, p=0.0091, Figure 8C) but no significant correlation was found in the pwMS population (*r*=0, p=0.97, Figure 8D).
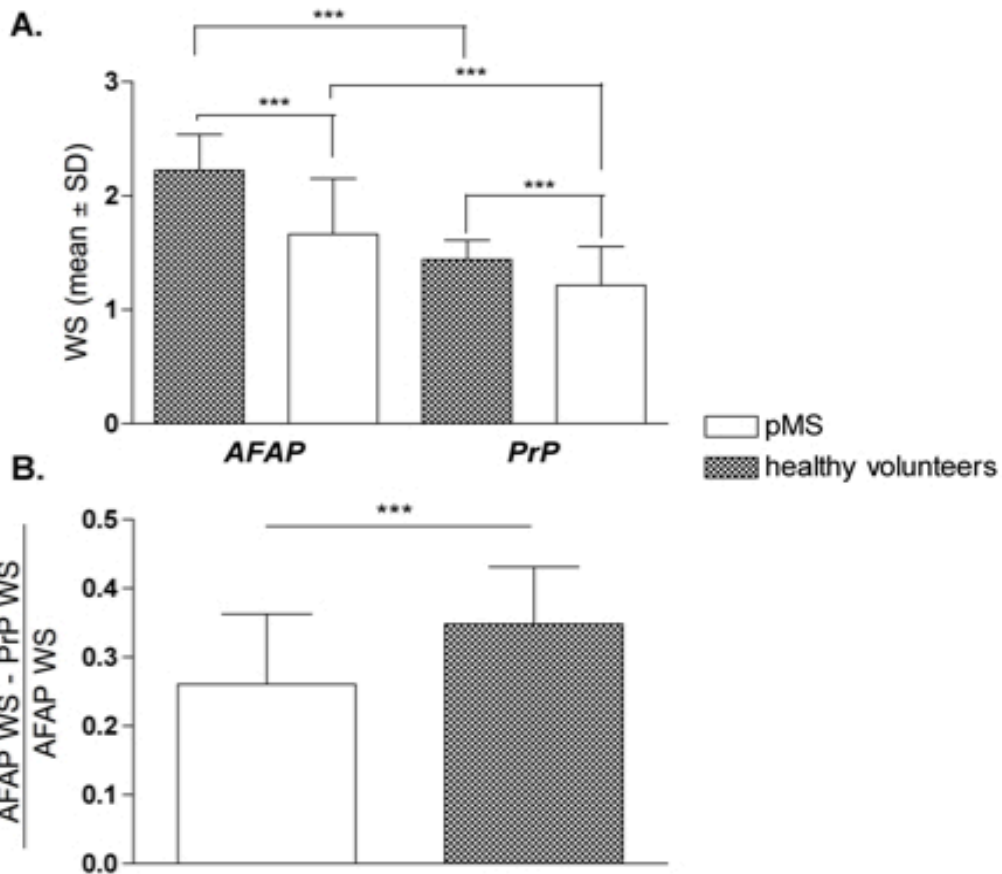
**Figure 6:** Mean walking speed (WS) in pwMS and healthy volunteers according to the "as fast as possible" (AFAP and the "preferred pace" (PrP) type of walk (A); relative difference between the AFAP and PrP WS in both populations (B).
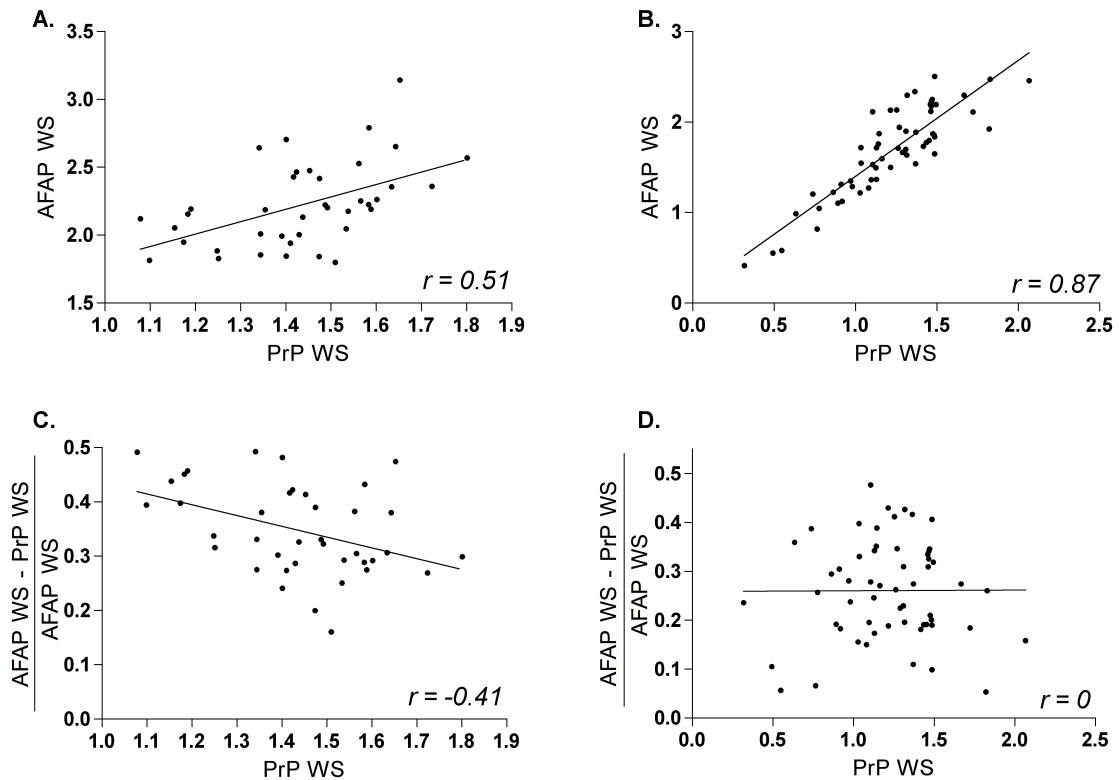


**Figure 7:** Correlations and linear regression between the walking speeds (WS) in the « as fast as possible » (AFAP) and the «preferred pace» (PrP) type of walk in healthy volunteers (A) and pwMS (B) ; correlation and linear regression between the relative difference AFAP-PrP and PrP WS in healthy volunteers (C) and pwMS (D).

### 3.3.4 Discussion

This cross-sectional retrospective work aimed to study the relationship between the WS that subjects tend to naturally adopt in the circumstances of a walking evaluation in a gait lab when asked to walk as comfortably as possible, and the WS they can achieve when asked to walk as fast as possible, which is the instruction usually given in routine clinical practice and in most clinical research settings, according to the guidelines for the administration of the T25FW (80).

The correlation between the WS measured according to both instructions was found to be higher in pwMS subjects than for healthy volunteers. One explanation for this finding would be that across the different pace one individual can naturally adopt, pwMS have a restricted range of possibilities, and tend to already walk nearby their maximum walking speed when walking in PrP. This assumption is supported by several other observations made in our cohort. First, there is a significantly lower relative difference between PrP and AFAP WS in pwMS as compared to healthy subjects. This finding disagrees with other reports which consider the slower WS of pwMS as an adaptive strategy to minimize the risk of fall due the neurological deficits (112). We alternatively consider the slower WS of pwMS as a consequence of cumulated neurological deficits rather than as a strategy preventing falls. An alternative hypothesis explaining this higher correlation would be that pwMS tend to already walk fast even when asked to walk comfortably. This could be explained by the stress induced in the gait lab. To test this hypothesis, measurement of PrP and AFAP WS in real life would be necessary but this raise the methodological question as to when, where and especially how to do this. Recently developed accelerometric techniques might be of particular interest for this purpose.

Second, no correlation could be found between PrP WS and the relative difference between PrP and AFAP WS in pwMS with a disability considered as moderate to high according to the EDSS. On the other hand, we believe that the demonstration of a moderately negative correlation between those parameters in the healthy volunteers population and pwMS with mild disability reflects a wider range of PrP WS accessible to subjects devoid of significant neurological impairment. The mechanisms regulating this PrP WS in healthy control is unknown, but one might hypothesize that psychological influences may have a role in addition to fitness and walking habits, and that the

somehow stressful environment of a gait lab might induce certain subjects to adopt a faster PrP WS, hence limiting their access to a higher WS when asked to walk AFAP.

## 3.4 Influence of manual rating on the results of distance-based walk tests

### 3.4.1 Introduction

Having examined the importance of the starting paradigm and of the instructed type of walk on the variability of walking speed measured along a distance of 25 feet, one potential strictly methodological bias remains unexplored: the influence of the precision of manual rating.

According to the MSFC guidelines, start and stop time must be recorded with a stop watch, when the lead foot crosses the starting or finishing lines of the distance walked. This procedure obviously tolerates a certain amount of error that is related to human imprecision because no other recording option is available. However, while usually considered insignificant, this assumption has never been truly quantified to our knowledge.

We thus proposed to evaluate the amount of error linked to the precision of a human rating in comparison with an automated system, hypothesising that manual rating would yield more imprecise results.

### 3.4.2 Methods

In healthy volunteers and pwMS, we prospectively collected and compared the manually and automatically measured walking times for 8 types of walk tests.

The gait analysis system, which will be described in detail later (see Part II), is based on range laser scanner technology. Briefly, the recorded signal allows to measure the position of both feet, with a spatial resolution of $\approx 1$ cm, and the walking times are measured with a resolution of 15 Hz. Start and stop times are defined as the instants at which the centre of the subject crosses the start and stop lines, respectively. The centre of the subject is defined as the point that is equidistant from its feet.

Eight walk tests were performed in the following order: the T25FW at a preferred pace, as fast as possible and in tandem gait (two times for each modality), a distance of 20 m following an 8-shaped trajectory (T20MW) performed once for each modality (preferred

pace, as fast as possible and tandem), a distance of 100 m performed once in « preferred pace » and once « as fast as possible » (T100MW) consisting of 5 laps of the 20 m trajectory and a distance of 500 m performed as fast as possible, consisting of 25 laps of the 20 m trajectory (T500MW). Manually measured times were obtained by a single rater who additionally recorded start and stop times according to the MSFC guidelines (81). Absolute differences between automated (AMT) and manually measured times (MMT) were calculated and expressed as their absolute value.

Statistical analysis and comparison of the results were realized with a one-way ANOVA test and post-hoc comparison were performed with 0.05 as a level of significance, using GraphPad Prism version 4.0b for Macintosh, GraphPad Software, San Diego California USA ([www.graphpad.com](www.graphpad.com)).

### 3.4.3 Results

Twenty-seven participants who performed a total of 648 walk tests were recorded. Participants included 24 healthy subjects (HV, 11 females, mean age 31 yo) and 3 pwMS (1 female, mean age 35 yo).

The mean absolute difference between the AMT and the MMT for all recorded tests was low with a value of $0.21 \pm 0.5$ (s, mean $\pm$ SD).
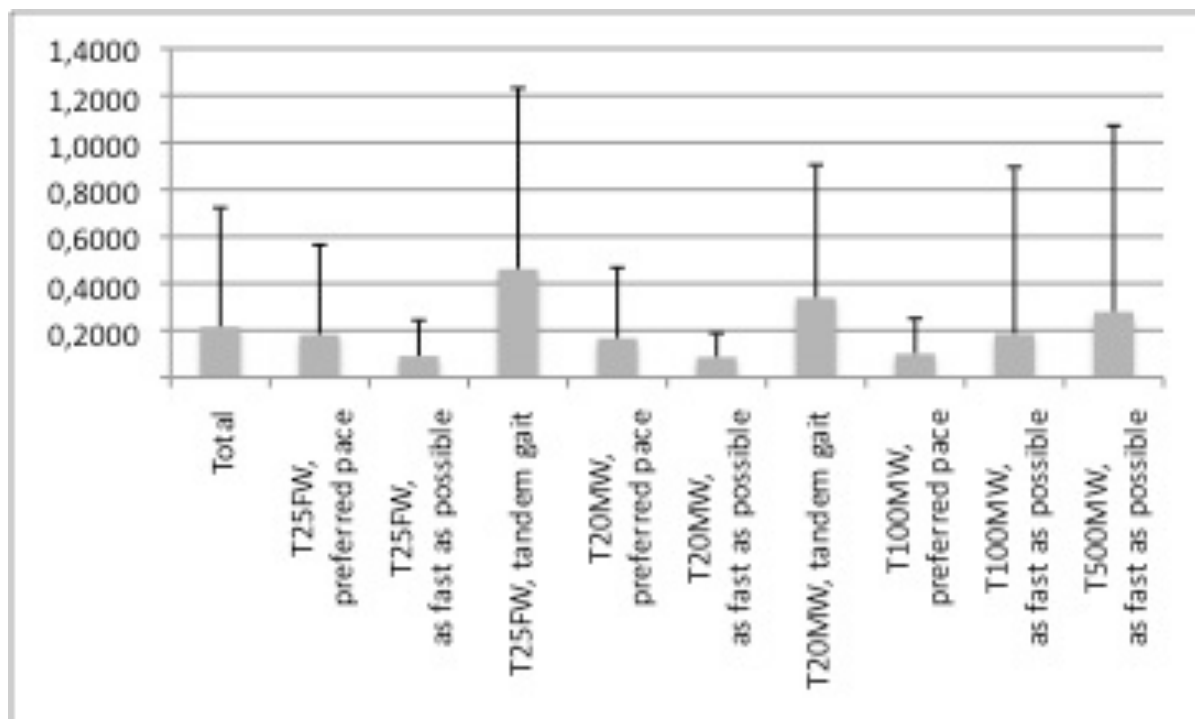


**Figure 8:** Absolute values of the mean absolute differences (in seconds, + SD) between the manual and automated measured times in different timed walked tests in a population of 24 healthy volunteers and 3 pwMS, across 9 walk tests.

The one-way ANOVA performed showed that the absolute AMT-MMT difference varied significantly when comparing the values of the 9 walk tests (F=5.7, df=8, p<0.0001). Post-hoc analysis showed significant differences only for the T25FW performed in tandem gait compared to the other tests (with the exception of the T20MW in tandem and the T500MW).

### 3.4.4 Discussion

In the present study we attempted to quantify the extent of imprecision related to manual measures in timed walked tests.

Two biases have to be kept in mind in the interpretation of our results. First, for methodological reasons, the automated measured times started and stopped according to the position of the centre of the subject (i.e., a point equidistant from its foot), which is different from the instructions of the MSFC, where start and stop times are recorded following the position of the leading feet. Second, it should be stressed that two different trajectories were used for the T25FW (straight path) and for the T20MW, the T100MW and the T500MW (8-shaped path), respectively. While these different trajectories probably have a minor influence on gait parameters, what will be discuss later, the start and stop positions of the subject are significantly different as related to the rater's position (see Fig 13). This might enhance the importance of the error of manual measure for the straight path where the start and stop lines are distant from the rater.

This second bias might explain the presence of significant differences between the AMT-MMT errors regarding the T25FW in tandem gait as compared to the other tests.

Overall, we observed only very small differences between automated and manual measures, and it can be concluded that the use of stopwatches as routine tools to measure walking speed seems reasonably reliable. When measuring walking speed with a stopwatch, particular attention should be paid to the placement of the rater near the start and stop lines of the walk test.

## 3.5 Motor Fatigue Measurement by Distance-Induced Slow Down of Walking Speed in Multiple Sclerosis

### 3.5.1 Introduction: Fatigue, the dark side of MS

Fatigue is a common symptom of MS that lacks a clear definition (113, 114) due to its multiple dimensions. It has been defined as an overwhelming feeling of tiredness without apparent reason and, in other contexts, as a reversible cognitive and motor impairment associated with a desire to rest, spontaneous or provoked by mental or physical activity, food ingestion, humidity or infection (115). More concisely, Barnett simply defined fatigue as a pathological exhaustion (116). Fatigue is described as more frequent in the progressive forms of MS, and may be influenced by the time of the day, sleep disorders (117), motor problems, pain syndromes, stress and mood disorders (118). However, pathological fatigue can be observed at any stage of the disease, sometimes independently from such factors.

Numerous hypotheses have been advanced to explain the pathophysiology of fatigue but none prevails.

The various and unclear definitions of fatigue in the literature have not much improved over the recent years probably because they reflect multiple dimensions enclosed within a single term. Psychological influences and consequences put aside, the major manifestations of fatigue in MS are cognitive and motor. Cognitive fatigue has been defined as a pathological decrease of cognitive performances along a sustained cognitive task. Its pathophysiology, evaluation and therapy are the subject of major fundamental and clinical research efforts, but are beyond the scope of this short introductory review.

Motor fatigability also holds different definitions but its manifestations probably make it the aspect of fatigue that is the most amenable to physiological measurement. Gandevia et al described it as a progressive, exercise-induced decline in voluntary activation of a muscle (119) and Schwid et al alternatively defined it as a loss of the maximal capacity to generate force during exercise (110). In MS, one of its manifestations is a decreased time to strength loss during sustained motor tasks as compared to healthy subjects (120). Motor fatigability is physiologically complex and remains partly unexplained

(121). It is considered as originating mainly from exercise-induced muscles changes in healthy subjects, and some anomalies distal to the neuromuscular junction have also been noted in the MS population (122, 123), although whether they are primary or secondary to other features of MS pathophysiology is debatable. Considering the multiple locations of lesions in MS, it is more than likely that CNS implication plays a role in the pathogenesis of motor fatigability (121). Sheean et al demonstrated using electrophysiological methods the implication of the CNS in pwMS motor fatigability. During a sustained contraction of the adductor pollicis, a progressive decline in central motor activation was recorded, and paralleled a decline in voluntary strength, with no change in the maximum strength generated by a direct ulnar nerve electrical stimulation (electrical twitch force), demonstrating the absence of significant changes at the peripheral level (120). These authors concluded that the failure of central motor drive to alpha motor neurons was responsible for the decline in central activation, although the mechanism of this failure remains unknown. Among the possible explanations for this phenomenon, the authors hypothesized that a dysfunction upstream to the primary motor cortex might be responsible. Interestingly, no correlation could be established between the electrophysiological alterations recorded during the motor task, and the subjective fatigue expressed by the subjects (expressed as a score measured by the Fatigue Severity Scale) or their EDSS. Very few studies have attempted to apply this type of research approach to motor fatigability at the level of the lower limbs (123), mainly because of methodological issues. Finally, there is no validated and routine clinical test to assess motor fatigability.

### 3.5.2 Measurement of locomotor fatigability with distance-based walking tests

Only few studies have investigated pwMS performances on longer distance walking tests, with variable results and methodologies, as well as small population samples (100, 110). Since our previous results led us to consider gait as a complex motor behaviour that can only be roughly disentangled by a single walking test, we hypothesized that a multimodal walking assessment of gait would allow a better delineation and quantification of functional gait impairment in pwMS (124).

In the present work, we developed a 500-meter walking test to evaluate the mean WS of pwMS in a demanding distance-based effort in comparison to the conventional short

distance 25-foot test in a similar "as fast as possible" type of walk. The distance of 500 m was chosen because it is a milestone of the EDSS (4.0) and since we previously observed a paradoxically high WS over a distance of 100 m, we felt a much longer distance was probably necessary to reach the threshold of motor fatigability in the majority of subjects. Our objectives were (i) to determine the range of performances of pwMS along this long-distance walking modality, (ii) to study the deceleration of the WS over this 500-meter distance in order to assess locomotor fatigability and (iii) to determine disease specificities that might be associated with locomotor fatigability by comparing different subsets of pwMS stratified according to their global EDSS, functional system (FS) scores (according to Kurtzke) and MrWD (below or above the 4000 m milestone).

### 3.5.3 Methods

The Ethics Committee of the CHU of Liège approved the study and written informed consent was obtained from all healthy subjects.

A total of 81 subjects with a diagnosis of relapsing or progressive MS according to the McDonald criteria (13) and a MrWD ≥ 500m, and 30 weight- and sex-matched healthy volunteers used as a control group were enrolled in the study. pwMS who had an EDSS from 4.5 to 6.0 were allowed to perform the walk tests using ambulatory assistive devices in case they would usually need it to walk the distance of 500 m or more. In such conditions (n=9), the only requirement was that they were asked to use the same device for all tests. Ankle–foot orthesis was permitted if worn from onset for all evaluations. pwMS who had experienced clinically disabling MS exacerbations with or without corticosteroid treatment within the last 3 months before study enrolment were excluded. Since it was previously shown that the time of the day does not significantly interfere with ambulation outcome performances despite changes in subjective fatigue (125), pwMS were tested at random periods of the day at their most convenient time.

pwMS and healthy controls performed a multimodal walking assessment that comprised 4 tests, in the following order : the T25FW (performed twice), the T25FW+ ((111), performed twice), the T100MW (126), and the Timed 500-Meter Walk Test (T500MW). A period of rest of 15 minutes was allowed between each test to minimize interference due to potential test-related fatigue, and all demanding physical activities (such as rehabilitation sessions) were suspended during 24 hours prior to the assessment. Our subjects did not report any increased sense of subjective fatigue before starting a new

test, especially before the last and most demanding T500MW. A slight worsening of the absolute results due to an increased motor fatigability in the T500MW could not be excluded but this methodological bias was identical for all subjects.

All assessments were made by a certified MS nurse or by a physical therapist in charge of pwMS' rehabilitation programs. Certified EDSS raters (RP, EL, VD or SB) collected all EDSS scores.

The MrWD was evaluated as described in (126).

The T25FW was performed according to the published standardized instructions (80).

The T25FW+ was performed as described in (111). In order to minimize test-retest variability, the mean value of the two tests was used in the analysis of the T25FW and the T25FW+.

The T500MW was performed as 5 non-stop consecutive laps of the same path that served for the T100MW, as described in (126), where interval times were recorded at each 100 m. The mean walking speed (MWS) expressed in meters per second was calculated by dividing 7.62 m (i.e. 25 foot), 100 m or 500 m by the time to perform the respective distances.

Comparisons between groups were made with unpaired student t-tests and comparison within group with paired t-tests. All statistical tests were applied with a two-tailed analysis and 0.05 as a level of significance and were performed using GraphPad Prism, version 4.0b for Macintosh, GraphPad Software, San Diego California USA (www.graphpad.com).

### 3.5.4 Results

The characteristics of HV and pwMS are detailed in Table VI. The distributions of gender and weight were comparable in both groups. The MS population was well balanced between different ranges of clinical disability stratified from EDSS 0 to 2.0, 2.5 to 3.5 and 4.0 to 6.0. Sixty per cent of our MS population had an unlimited walking range defined by a MrWD ≥ 4000 m, whereas approximately 40% reported to be able to walk between 500 m and 4000 m. pwMS were also stratified according to pyramidal, cerebellar and sensitive Kurtzke FS scores (all FS≤1, FS=2 or FS=3, no pwMS had an FS>3 in one of these three systems).

**Table VI:** Characteristics of pwMS and healthy volunteers

| | pwMS | Healthy controls |
|---|---|---|
| Number | 81 | 30 |
| Age (years; mean ± SD) | 40.16 ± 11.35 | 30.3 ± 10.4 |
| Sex (female. %) | 59 | 70 |
| BMI[1] (mean ± SD) | 23.72 ± 4.13 | 23.33 ± 3.37 |
| MS type (CIS/RR/SP/PP[2]. %) | 10.1/61.7/14.6/13.4 | n.a. |
| Disease duration (years; mean ± SD) | 9.75 ± 8.79 | n.a. |
| EDSS[3] (median; range) | 3.5 (0-6.0) | n.a. |
| 0-2.0 (n. %) | 30, 37 | n.a. |
| 2.5-3.5 (n. %) | 21, 25.9 | n.a. |
| 4.0-6.0 (n. %) | 30, 37 | n.a. |
| All FS[4] ≤ 1 (n, %) | 21, 25.9 | n.a. |
| FS Pyramidal = 2, irrespective of other FS (n, %) | 15, 18.5 | n.a. |
| FS Cerebellar = 2, irrespective of other FS (n, %) | 18, 22.2 | n.a. |
| FS Sensitive = 2, irrespective of other FS (n, %) | 34, 41.9 | n.a. |
| FS Pyramidal = 3, irrespective of other FS (n, %) | 25, 30.9 | n.a. |
| FS Cerebellar = 3, irrespective of other FS (n, %) | 31, 38.3 | n.a. |
| FS Sensitive = 3, irrespective of other FS (n, %) | 15, 18.5 | n.a. |
| MrWD[5] | | |
| ≥ 4000 m (n, %) | 49, 60.5 | n.a. |
| ≥ 500 m ; < 4000 m (n, %) | 32, 39.5 | n.a. |

1; Body Mass Index (kg/cm²); 2: clinically isolated syndrome/ relapsing-remitting/ secondary progressive/ primary progressive - progressive-relapsing; 3: Expanded Disability Status Scale; 4: Kurtzke Functional System Scores; 5: Maximum reported Walking Distance
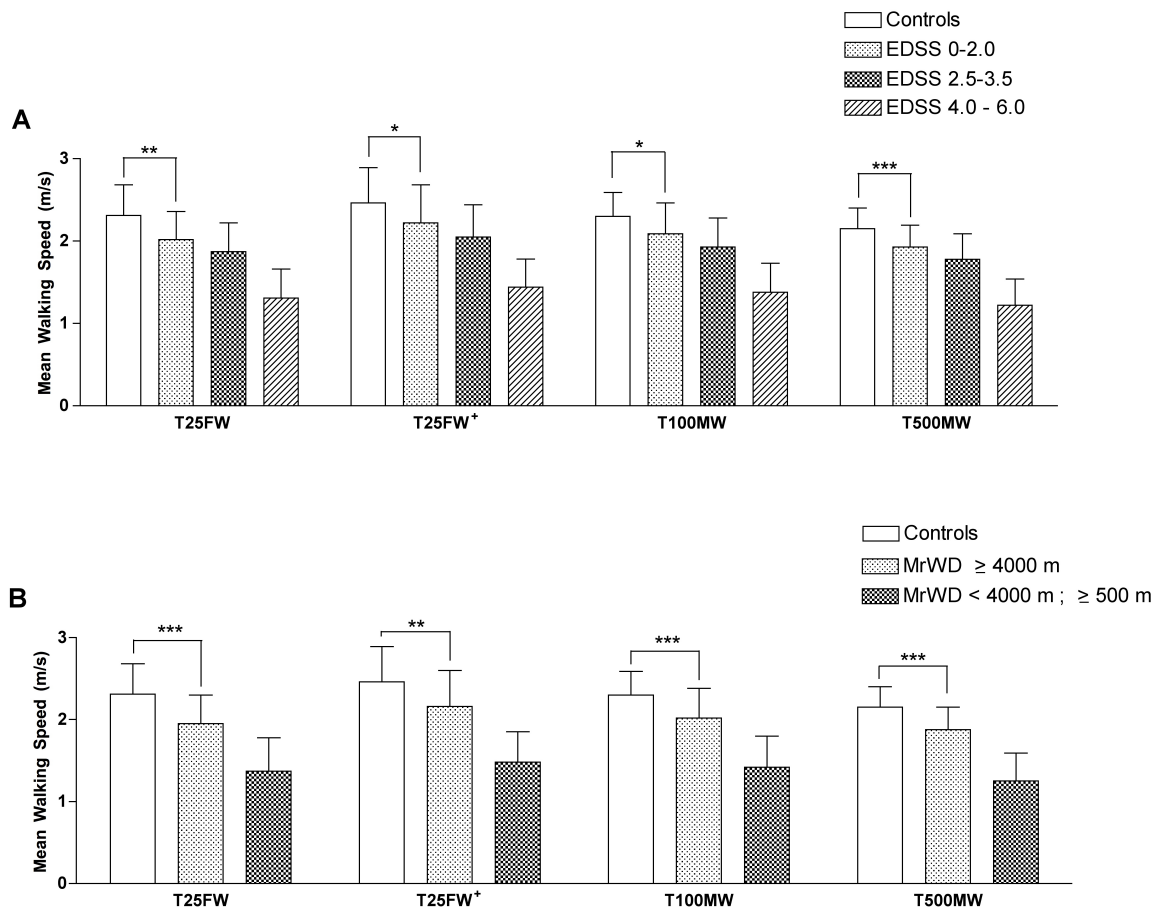
**Figure 9. Mean walking speed (MWS) in healthy volunteers and different subgroups of the pwMS population.** The same general pattern of MWS differences across the different walking paradigms is observed in every group (T25FW+>T100MW>T25FW>T500MW). In the 4 walking tests, the MWS was significantly slower for each subset of the pwMS population compared to healthy volunteers (all p<0,0001), including pwMS with a low level of disability according to their EDSS status (EDSS≤2.0, A) or an apparently unlimited MrWD (MrWD≥4000m, B).

Mean timed performances in the 4 walking tests (with time laps of the T500MW) for healthy volunteers and for the different subgroups of pwMS are presented in Table VII. The mean WS was compared between the 4 tests (Figure 9) in HV and pwMS according to their EDSS and MrWD. In healthy volunteers and in all subsets of pwMS regardless of their EDSS or MrWD status, the order of calculated mean WS values was T25FW+ > T100MW > T25FW > T500MW. In all walking tests, the WS was significantly lower for each subset of the pwMS population compared to HV (statistics only shown graphically in Fig. 9A and 9B for pwMS with an EDSS ≤ 2.0 or an apparently unlimited MrWD ≥ 4000 m). WS was also significantly lower for pwMS at EDSS 4.0–6.0 compared to EDSS 2.5–3.5, in the 4 walking tests (Figure 9A, p<0.001 for all comparisons).

**Table VII:** Timed Performances[1] of Respective Populations in the Different Walking Tests

| | Controls | pwMS All (81) | EDSS 0-2.0 (30) | EDSS 2.5-3.5 (21) | EDSS 4.0-6.0 (30) | MrWD≥4000 (49) | MrWD 500 – 4000 (32) |
|---|---|---|---|---|---|---|---|
| T25FW[2] | 3,38 ± 0,53 | 4,91 ± 2,10 | 3,88 ± 0,64 | 4,21 ± 0,76 | 6,44 ± 2,73 | 4,04 ± 0,77 | 6,25 ± 2,72 |
| T25FW[+3] | 3,17 ± 0,48 | 4,42 ± 1,57 | 3,57 ± 0,69 | 3,85 ± 0,77 | 5,66 ± 1,82 | 3,67 ± 0,74 | 5,56 ± 1,80 |
| T100MW[4] | 44,05 ± 5,50 | 61,26 ± 22,59 | 49,23 ± 8,27 | 53,69 ± 10,50 | 78,59 ± 27,60 | 51,02 ± 9,60 | 76,94 ± 27,48 |
| T500MW[5] | 235,28 ± 27,80 | 338,32±134,23 | 265,25 ± 44,89 | 289,50 ± 53,66 | 445,56 ±162,97 | 272,28 ± 43,49 | 439,44 ± 161,43 |
| 0-100 | 45,29 ± 5,87 | 63,08 ± 22,03 | 50,05 ± 8,35 | 55,23 ± 10,32 | 81,59 ± 24,91 | 51,86 ± 9,10 | 80,26 ± 24,90 |
| 100-200 | 46,97 ± 6,92 | 67,15 ± 25,55 | 53,14 ± 8,16 | 57,96 ± 12,27 | 87,59 ± 30,57 | 54,45 ± 8,37 | 86,59 ± 30,52 |
| 200-300 | 47,81 ± 5,30 | 67,91 ± 26,45 | 53,86 ± 8,00 | 58,73 ± 10,72 | 88,39 ± 32,98 | 55,42 ± 8,50 | 87,05 ± 32,70 |
| 300-400 | 48,14 ± 5,83 | 69,36 ± 22,03 | 54,18 ± 10,25 | 58,87 ± 11,34 | 91,89 ± 35,63 | 55,48 ± 9,37 | 90,62 ± 35,36 |
| 400-500 | 47,08 ± 5,36 | 70,82 ± 33,41 | 54,02 ± 11,37 | 58,70 ± 9,84 | 96,10 ± 42,70 | 55,08 ± 9,09 | 94,92 ± 41,37 |
| | All FS ≤ 1 (21) | FS P=2 (15) | FS P=3 (25) | FS C=2 (18) | FS C=3 (31) | FS S=2 (34) | FS S=3 (15) |
| T25FW[2] | 3,80 ± 0,57 | 4,62 ± 1,10 | 6,62 ± 2,93 | 4,24 ± 0,83 | 6,40 ± 2,69 | 4,74 ± 1,59 | 7,08 ± 3,37 |
| T25FW[+3] | 3,48 ± 0,67 | 4,20 ± 0,91 | 5,78 ± 1,94 | 3,89 ± 0,73 | 5,66 ± 1,80 | 4,30 ± 1,20 | 6,12 ± 2,26 |
| T100MW[4] | 48,04 ± 7,39 | 58,20 ± 13,16 | 80,80 ± 29,24 | 52,96 ± 9,01 | 78,86 ± 27,10 | 60,29 ± 18,37 | 83,43 ± 34,25 |
| T500MW[5] | 254,86 ± 29,69 | 320,97±76,14 | 456,92±173,69 | 291,83 ± 60,60 | 446,01±158,83 | 336,86±115,79 | 467,63 ± 196,46 |
| 0-100 | 48,48 ± 7,43 | 61,81 ± 16,02 | 83,03 ± 25,99 | 55,27 ± 10,71 | 81,75 ± 24,14 | 62,85 ± 19,98 | 85,54 ± 28,51 |
| 100-200 | 51,37 ± 4,96 | 65,48 ± 16,90 | 88,72 ± 32,74 | 57,68 ± 11,63 | 88,13 ± 29,79 | 67,03 ± 23,19 | 92,11 ± 35,75 |
| 200-300 | 52,07 ± 5,85 | 64,63 ± 14,48 | 90,64 ± 35,27 | 58,98 ± 11,35 | 88,41 ± 32,22 | 67,11 ± 21,49 | 94,18 ± 40,53 |
| 300-400 | 51,62 ± 5,93 | 64,33 ± 14,94 | 94,76 ± 38,06 | 59,98 ± 13,44 | 91,90 ± 34,79 | 68,54 ± 23,09 | 96,59 ± 44,1 |
| 400-500 | 51,33 ± 7,11 | 64,71 ± 15,34 | 99,77 ± 45,38 | 59,92 ± 14,34 | 95,82 ± 41,79 | 71,33 ± 31,39 | 99,21 ± 48,64 |

1 : each time performance is expressed in seconds, as mean ± SD ; 2 : Timed 25-Foot Walk Test ; 3 : Corrected version of the T25FW with a dynamic start ;
4 : Timed 500-Meter Walk Test with lap times evaluated for every 100 meter interval

No significant difference was found between the WS of the pwMS at EDSS 0–2.0 compared to EDSS 2.5–3.5 (p=0.1419 for T25FW, p=0.1987 for T25FW+, p=0.1178 for T100MW, and p=0.0783 for T500MW). Finally, WS was significantly higher for pwMS with an MrWD ≥ 4000 m compared to that of pwMS with an MrWD < 4000 m in the 4 walking tests (Figure 9B, p<0.001 for all comparisons). When pwMS were stratified according to pyramidal, cerebellar and sensitive Kurtzke FS scores, WS data for all walking tests were very sensitive to detect significant differences between pwMS with all FS ≤ 1 and pwMS with at least one FS=2 or to detect significant differences between pwMS with one FS=2 and pwMS with the same FS=3 (Table X).

In the T500MW, WS was calculated over the five successive 100 m interval laps in order to capture the motor fatigability related deceleration occurring over time during this demanding motor task (Table VII, Figure 10). Different patterns of mean WS evolution were observed as a function of the type of population studied (Figure 10). Regardless of the absolute differences of their MWS, healthy volunteers and pwMS with a low level of disability (i.e. with an EDSS ≤ 2.0, MrWD > 4000 m or all FS scores ≤ 1, Figure 10A, 10B and 10C, D, E, respectively) significantly decelerated during a 500 m walking task, as demonstrated by the comparison between the mean WS of the first 100 m (T0–100MW) and the mean WS of the last 100 m (T400–500MW) during the test (p=0,0104 for healthy volunteers, p<0,0001 for pwMS with MrWD≥4000 m and p=0,0089 for pwMS with all FS scores ≤ 1). A mild acceleration at the end of the task (i.e. a higher WS during the last 100 m - T400–500 - compared to the WS over the T300–400) was observed in healthy volunteers and pwMS with all FS scores ≤ 1, but reached significance only in the healthy volunteers population (p=0,0286, data not shown). A highly significant deceleration was consistently observed in more disabled pwMS with an EDSS 2.5–3.5 and 4.0–6.0 (Figure 10A), a MrWD between 500 and 4000 m (Figure 10B) or Kurtzke FS scores at 2 or 3 in the pyramidal, cerebellar or sensitive systems (Figure 10C, D and E, respectively). For these latter more disabled pwMS groups all p values were < 0,0001 for the comparisons of WS between T0–100MW and T400–500MW.

In order to quantify ambulation fatigability over a demanding distance of effort, we proposed to integrate the fastest and the lowest measurable walking speeds over the different tested walking paradigms. The T25FW+ WS was previously confirmed to be a valid test to approach the fastest WS of pwMS on a very short distance regardless of heir acceleration capacity (111).

**Table X** : Statistical comparisons of the walking speed in the 4 walk tests across different subsets of the pwMS population

| | FS P | | FS C | | FS S | |
|---|---|---|---|---|---|---|
| | **2** | **3** | **2** | **3** | **2** | **3** |
| **T25FW** | | | | | | |
| **All FS≤1** | 0.0141* | n.d. | 0.1036 | n.d. | 0.0075** | n.d. |
| **P2** | n.d. | 0.0009*** | n.d. | n.d. | n.d. | n.d. |
| **C2** | n.d. | n.d. | n.d. | P<0.0001*** | n.d. | n.d. |
| **S2** | n.d. | n.d. | n.d. | n.d. | n.d. | 0.0003*** |
| **T25FW⁺** | | | | | | |
| **All FS≤1** | 0.0198* | n.d. | 0.0911 | n.d. | 0.0057** | n.d. |
| **P2** | n.d. | 0.0004*** | n.d. | n.d. | n.d. | n.d. |
| **C2** | n.d. | n.d. | n.d. | P<0.0001*** | n.d. | n.d. |
| **S2** | n.d. | n.d. | n.d. | n.d. | n.d. | 0.0003*** |
| **T100MW** | | | | | | |
| **All FS≤1** | 0.0137* | n.d. | 0.0918 | n.d. | 0.0037** | n.d. |
| **P2** | n.d. | 0.0004*** | n.d. | n.d. | n.d. | n.d. |
| **C2** | n.d. | n.d. | n.d. | P<0.0001*** | n.d. | n.d. |
| **S2** | n.d. | n.d. | n.d. | n.d. | n.d. | 0.0015** |
| **T500MW** | | | | | | |
| **All FS≤1** | 0.0012** | n.d. | 0.0211* | n.d. | 0.0004 | n.d. |
| **P2** | n.d. | 0.0003*** | n.d. | n.d. | n.d. | n.d. |
| **C2** | n.d. | n.d. | n.d. | P<0.0001*** | n.d. | n.d. |
| **S2** | n.d. | n.d. | n.d. | n.d. | n.d. | 0.0009*** |

On the other hand, the mean finishing pace during the last 100 m of the T500MW (T400–500MW) appeared to be the lowest measure in the range of walking speeds observed in the different tests administered (Figure 10). The difference between T25FW⁺ WS and T400–500MW WS was significant in all pwMS subgroups and healthy volunteers (Figure 11A, all p<0.0001). The individual performances of pwMS showed that the relative deceleration observed between WS values of the T25FW⁺

**Figure 10. WS calculated over five successive 100m-interval laps along the T500MW.** Subgroup analysis are presented in healthy volunteers and in different subgroups of the pwMS population, stratified according to their EDSS (**A**), their maximum reported walking distance (MrWD) (**B**), and their pyramidal (**C**), cerebellar (**D**) and sensitive (**E**) functional scores (FS). The dashed lines represent the comparison between the "baseline" mean WS of the first 100m (T0-100MW) and the "final" mean WS of the last 100m (T400-500MW) for all subgroups. t-test values were *p<0.05, **p<0.01, ***p<0.0001



68
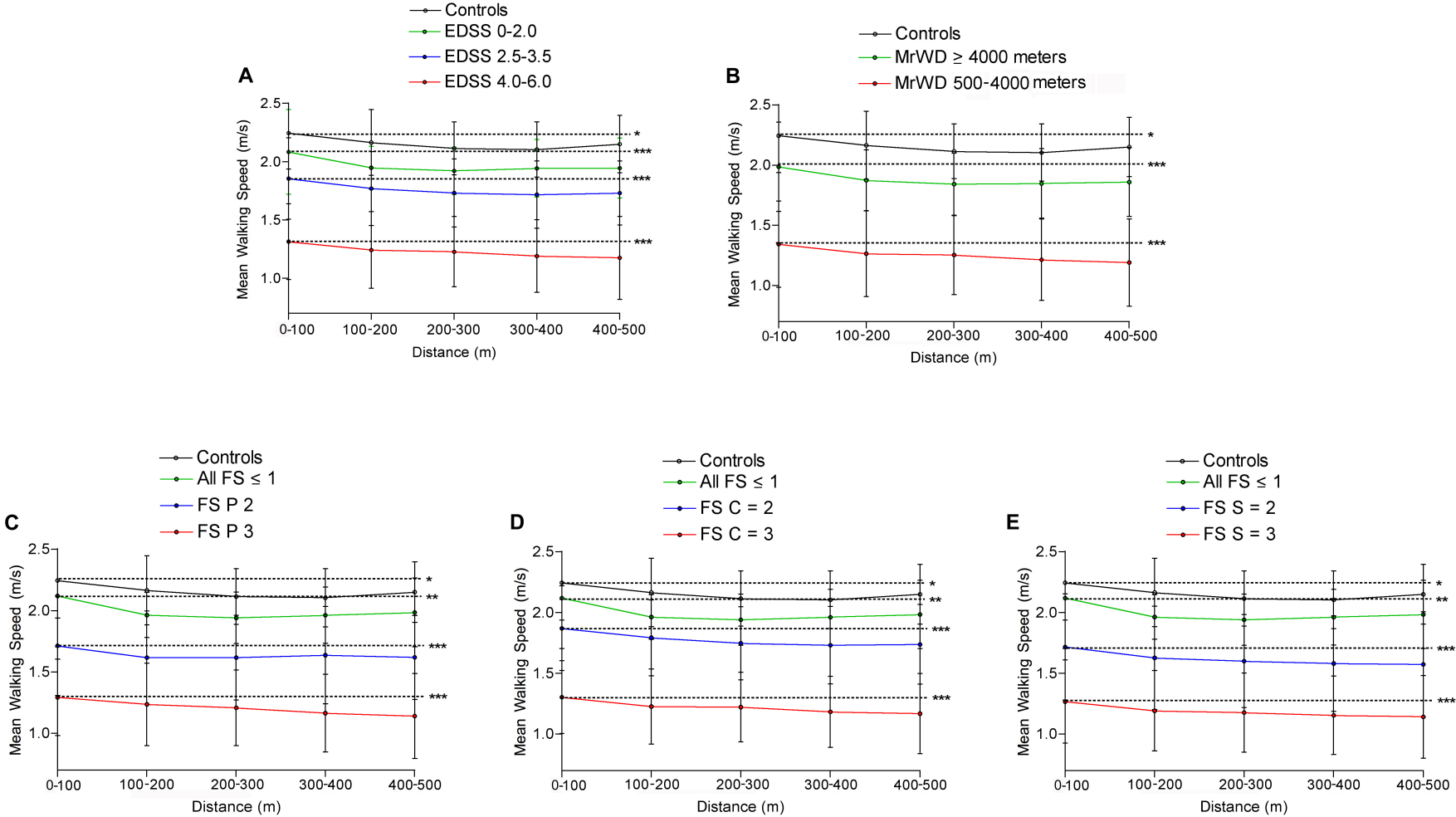
and T400–500MW (expressed as percentage of the T25FW$^+$ mean WS) was highly variable at all levels of walking impairment (stratified according to the T25FW, Figure 11B) and EDSS status (Figure 11C). We calculated a Deceleration Index (DI) as the ratio between mean WS of the T400–500MW divided by mean WS of the T25FW$^+$ (Figure 11D). Hence, the lower the DI ratio is, the more pronounced the pwMS were subjected to fatigue-related decrease of their walking speed over a long distance effort evaluated here by a 500 m task. We observed a non-significantly lower DI for pwMS altogether compared to healthy controls (p=0.088). pwMS with an EDSS 4.0–6.0 had a significantly lower DI compared to pwMS with an EDSS ≤ 2.0 (p=0.045). Compared to pwMS with pyramidal, cerebellar and sensitive FS scores all ≤ 1, pwMS with pyramidal or cerebellar FS at 2 had a non-significantly lower DI (p=0.33 and p=0.42, respectively), whereas pwMS with pyramidal or cerebellar FS at 3 had a significantly lower DI (p=0.02 and p=0.03, respectively). In contrast, pwMS with a sensitive FS at 2 or 3 had a lower DI than pwMS with all FS scores ≤ 1 but the differences were not significant for both comparisons. The DI of pwMS subjects with a MrWD between 500 m and 4000 m was significantly lower than for pwMS with a MrWD ≥ 4000 m (p=0.0044). Finally, in contrast to the differences measured over absolute walking performances in short or long distance walking tests, no significant differences were observed for DI values between healthy volunteers and pwMS with a low level of disability (i.e. with an EDSS ≤ 2.0, MrWD ≥ 4000 m or all FS scores ≤ 1, statistics not graphically shown on Figure 11D).

### 3.5.5  Discussion

This study evaluated the relative walking speed performances of pwMS compared to healthy volunteers on short and long distance walking tests. The groups were well matched according to BMI and sex ratio but the higher age in the pwMS population compared to healthy volunteers may have influenced the observed differences since the mean WS probably decreases with age (89). All walking tests were performed in the "as fast as you can" configuration of the task in order to downsize motivational interferences, which are probably more prominent in a "preferred pace" modality (127), at least in healthy subjects and pwMS with mild disability.

We demonstrate that in a cohort of pwMS with mild to moderate disability and EDSS scores ranging up to 6.0, the evaluation of walking capacities over 500 m was an achievable goal, as long as assistive devices and short stops if needed were allowed for

the more disabled pwMS with EDSS between 4.5 and 6.0. The range of performances of our pwMS population was globally in line with that of previous studies evaluating walking speed on similar distances (92, 100, 110).

The absolute performances of pwMS obviously decreased according to the EDSS score, but a significant ambulation impairment was already seen on short and long distance in pwMS with mild disability, with an EDSS status ≤ 2.0 or a MrWD ≥ 4000 m (103, 106).

We observed various patterns of deceleration in the different subsets of pwMS over a 500 m walking task, regardless of absolute timed performances. As previously described, healthy volunteers and pwMS with minimal disability (all FS scores ≤ 1, i.e. EDSS ≤ 1.5) retained the ability to accelerate during the last 100 m of the 500 m task (100, 110). This final WS acceleration referred to the comparison between the T400–500 and the T300– 400. However the mean WS of the T400–500 remained significantly lower than the mean WS of T0–100 for all subgroups. This observation is probably related to motivational issues ("end of the task" phenomenon, since we here used 100 m laps), but it is striking that no final WS acceleration was observed in more disabled pwMS, which may reflect the consequences of an increased corticospinal dysfunction or a more severe cognitive impairment – referring to a dysfunction upstream to the primary motor areas as previously suggested in (120) – or both. For pwMS with significant disability ranging from EDSS 2.5 to 6.0, the finishing pace of the last 100 m of the T500MW was the slowest measurable WS across the 4 walking tests. In contrast, the mean WS on T25FW+ with a propelled start provided the fastest measurable WS in all pwMS subgroups.

In order to assess locomotor fatigability, we identified the deceleration index (DI) as a ratio between the minimal (T400–500) and maximal (T25FW+) measurable WS. The origin of walking fatigability was not investigated in this study, but it is noteworthy that pwMS with a value of 3 on pyramidal or cerebellar FS scores demonstrated a significant alteration in the DI whereas pwMS with a value of 3 on sensitive FS score did not. The individual DI of pwMS were highly variable at all stages of walking impairment and the mean DI was significantly lower only in pwMS with EDSS 4.0–6.0 or a maximum reported walking distance < 4000 m. The mean DI remained similar to healthy volunteers in pwMS with a low level of disability (i.e. with an EDSS ≤ 2.0, MrWD ≥ 4000 m) while absolute walking performances on short or long distance walking tests were all significantly abnormal in these pwMS subgroups at early disease stages.

**Figure 11. Quantification of ambulation fatigability with the Deceleration Index**. Ambulation fatigability was evaluated through the integration of the fastest (T25FW[+]) and the lowest (T400-500MW) measurable WS, which were obviously highly statistically different in all pwMS subgroups and healthy volunteers (**A**, all $p < 0,0001$). No significant correlation could be found between the individual values of relative deceleration evaluated by the difference of mean WS on the T25FW[+] and on the T400-500MW (expressed as percentage of the T25FW[+] mean WS) and the level of walking impairment according to the T25FW (**B**) or the EDSS status (**C**). Deceleration Index (DI) calculated as the ratio between mean WS of the T400-500MW divided by mean WS of the T25FW[+] (**D**) in healthy volunteers and in different subgroups of the MS population.
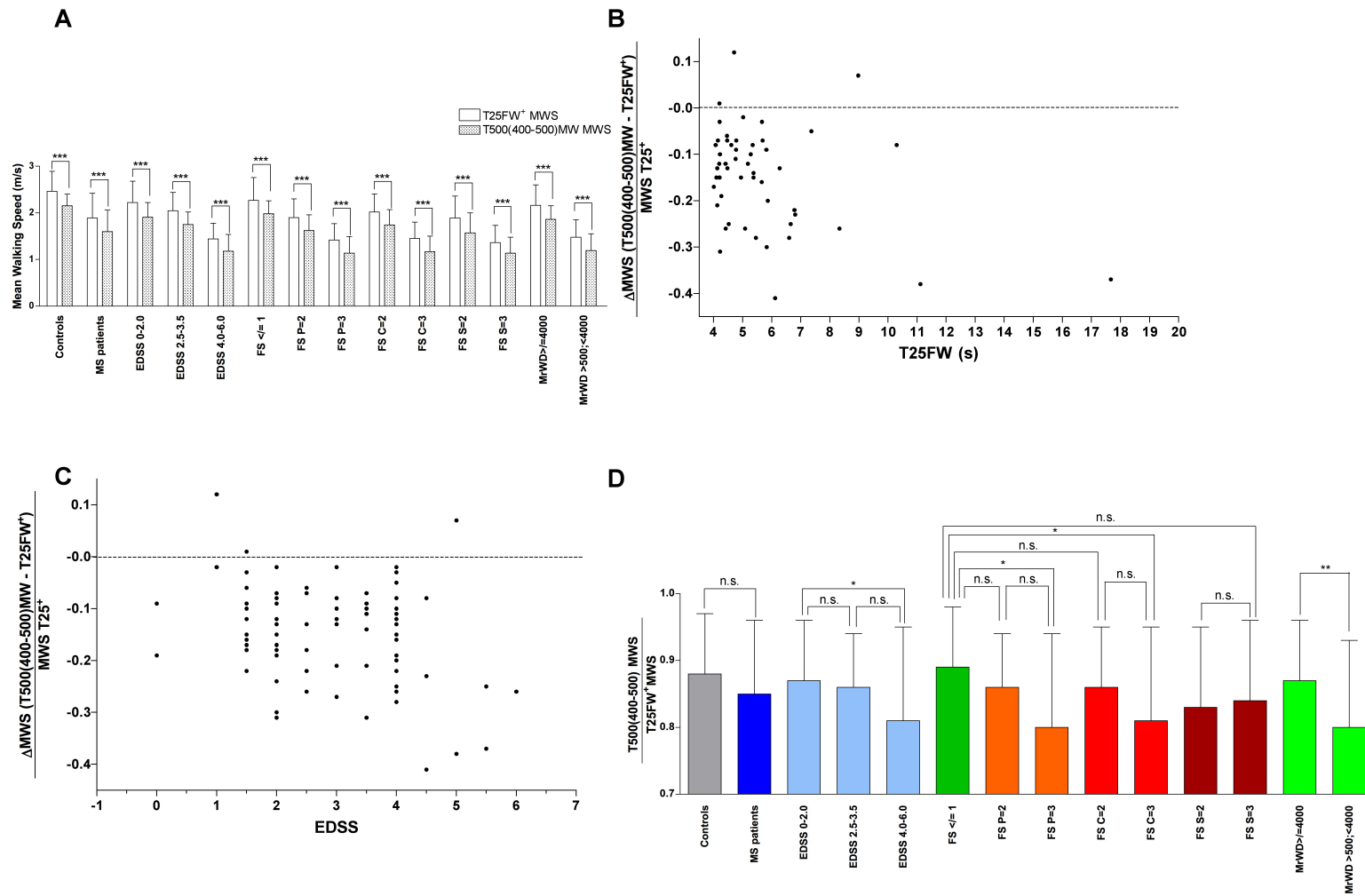
These results indicate that DI measures the alteration of a sustained motor performance throughout a long demanding walking task, which is not captured by conventional absolute WS measurements, whether on a specific short or long distance, or in time-based settings. Such findings are consistent with the previous demonstration that motor fatigability is partially independent from motor (pyramidal) weakness (110, 120, 128).

In regard of the usual 500 m MrWD delineated by the EDSS calculation rules, this work suggested that a MrWD of 4000 m may be a more reliable threshold to better discriminate between "fully ambulatory" (as termed by John F. Kurtzke) and significantly limited pwMS according to their walking performances. Although the 4000m were somehow chosen arbitrarily, a higher threshold might have led to consider healthy untrained individuals as disabled. It was outside the scope of the present cross-sectional analysis to investigate the sensitivity to change of the walking tests and their relevance in self-reported quality of life of pwMS.

In conclusion, we provide evidence that sequential gait evaluation over a 500 m distance is a valuable tool to measure the decrease of WS over the duration of a demanding walking task. The combination of short and long distance "as fast as possible" walking tests to assess a relative deceleration (DI) is a coherent paradigm to allow a reliable measurement of locomotor fatigability. Our data suggest that ambulation fatigability is at least partially independent from absolute performances on a given distance, which are abnormal early in MS, while the DI is altered with more advanced disability statuses. The DI may be a sensitive tool to detect and measure walking fatigability even though it is less sensitive than absolute mean WS on short and long distances to detect early walking impairment.

## 3.6 Conclusions

In this first part of our work, we evaluated the impact of potential confounding factors in the evaluation of walking speed in persons with MS.

First we showed differential effects of the chosen distance. We demonstrated that the evaluation of WS over 100 m with the Timed 100-Meter Walk test was achievable and displayed modest qualities favouring its use over the T25FW, such as a slightly better test-retest ICC, lower variability and better correlation with the maximum reported walking distance. Paradoxically, a significantly higher WS was observed during the T100MW compared to the T25FW. This reinforced our conception that a short walking distance such as 25 feet was not sufficient to properly monitor the « maximum » WS a subject can achieve and the necessity to further evaluate other confounders of WS measurement.

Second, we showed that the first meters of the 25 feet distance during which the subject accelerates accounted for up to 10% of the measured WS, and that this influence was significantly higher in pwMS, suggesting a possible alteration of acceleration capacity related to MS. The mechanisms underlying this observation remains uncertain, and future works addressing the influences of physical or cognitive disability, as well as fatigue, will provide insights into their pathophysiology, while targeted postural and gait evaluations will help to better explain the altered dynamic of the acceleration process.

Third, we characterized how the instructed type of walk, i.e. « as fast as possible » vs. « preferred pace » can differentially influence the WS, with a poorer ability of more disabled MS population to gain speed over their baseline WS as compared to normal subjects and pwMS with mild disability. This questions the mechanisms regulating the preferred walking speed, the capacity to accelerate and their potential alteration in MS. Here also, our findings might benefit from a deeper analysis of cognitive, psychological and fatigue dimensions.

Finally, we investigated the decrease of WS over a 500 m task and observed different patterns of deceleration according to the degree of disability of subjects. In order to emphasize the importance of WS deceleration, we proposed to combine the results of the maximum and minimum measurable WS in a Deceleration Index. We observed evidences suggesting that this DI is a measure representative of locomotor fatigability, which is part of a dimension of MS that remains difficult to quantify in routine clinical

practice. Future works should study the relationship between locomotor fatigability as represented by this DI and other dimensions of fatigue, whether subjective such as patient-reported fatigue scales, or objective such as electrophysiological studies (120, 129) or MRI evaluations (130).

It should be kept in mind that the present findings and raised questions were all drawn from measures of gait speed according to various methodologies, which is in line with our first objective. However, other gait disturbances that are usually encountered during the course of MS were not taken into account. This is why we moved to our second objective: studying gait of pwMS with tools that are sensitive to other gait descriptors than the sole walking speed.

# 4 Part II: Development a new tool to measure gait dysfunction in pwMS to cross the line of walking speed

## 4.1 Introduction

Although our previous work helped to identify the main factors implicated in the regulation of WS in pwMS as measured on a short distance, we have not yet investigated the implication of other features than WS in gait analysis and quantification. It is therefore possible that various phenomena (deceleration and fatigue, acceleration, gait performances across preferred or rapid pace) we inferred from changes in walking speed observed in different timed walk tests are better explained by changes in gait dynamics we were not able to capture. For example, ataxia and spasticity (50, 51), which are frequent in MS, may not be taken into account by « conventional » evaluations of gait. Moreover, their relationship to walking speed decrease and locomotor fatigability has been poorly studied in neurology, including in the field of MS (131). Beyond better insights into the pathophysiology of gait dysfunction (and thus its neural correlates), an advanced knowledge of abnormal patterns of gait may also help to guide each steps of rehabilitating interventions. Lack of insights into the mechanisms of gait dysfunction is mainly due to a lack of tools able to measure characteristics of gait that might be representative of specific clinical alterations. While such tools do actually exist, most are not easily accessible to routine clinical practice or multicentre trials, because they are either too time-consuming, expensive or yield results not readily accessible to lay physicians, who are not familiar with specialized descriptive gait analysis.

In order to explore the participation of other features than WS alone to the alteration of gait in MS, we aimed to develop a gait analysis system that would circumvent these limitations without loosing the advantages of established techniques. These will now be briefly described with respect to their application in MS.

### 4.1.1 Walking mats

Givon et al have characterized the spatio-temporal parameters of gait in MS using the GAITrite functional ambulation system (132). The GAITrite is a walking mat with sensors arranged in a grid-like pattern allowing the identification of footfall contacts.

Using this technology to compare 81 pwMS and 25 healthy volunteers who walked for a distance of 4.6 m over the device, the authors concluded that pwMS walked more slowly, with a lower cadence (steps/min), shorter steps, a shorter step time and a wider step width. They also showed a positive correlation of the double support time with the EDSS and the pyramidal functional score, as well as of the base of support width with the EDSS and the cerebellar functional score. Furthermore, differences in gait descriptors between purely cerebellar and purely pyramidal pwMS were demonstrated: purely pyramidal subjects walked with a decreased gait speed, step length, single support and swing time while purely cerebellar subject walked with a wider base of support and a shorter swing time. This study provided however no information on the potential link between the reported alterations and walking speed. Moreover, two major issues can be raised concerning the GAITrite technology itself: (i) this system only studies the foot contact with the ground while no information is obtained regarding the foot trajectory during the stepping process and (ii) the length over which the gait descriptors are recorded is usually limited, i.e. 4.6 m in the present study, with a mean number of step taken by the participants of 10. This represents barely more than half of the standard distance of 25 feet in multiple sclerosis.

## 4.1.2 Accelerometers

Accelerometers are low-cost devices that can be fixed on any chosen body part and provide an approximate measure of its mobility. In Parkinson's disease, Stamatakis et al have used 4 accelerometers (2 per feet) to allow a precise temporal delineation of stepping times, gait initiation and detection of freezing (133). Such configurations have not been proposed in MS, where most studies use one device fixed as close as possible to the subject's centre of mass. This enables the approximation of whole body movements with minimal noise. Motl et al studied the accuracy of the Actibelt® accelerometer for measuring walking speed of 51 pwMS with a wide range of disability (according to the EDSS) in a controlled setting. They found that the Actibelt® measured accurately walking speed during the 6 minute walking test, although it tended to significantly overestimate it, especially in pwMS with an EDSS ≥ 4.0, as compared to the manual measurement of walking times (134). In our view, the major advantage of accelerometers is the possibility to measure physical activity in subjects' real life, outside of the controlled setting of gait labs, and on longer distances. Sosnoff et al

validated this possibility by studying accelerometric data of 70 pwMS recorded for 7 consecutive days and collected during the waking hours (135). They demonstrated that significant differences existed in total daily movements between pwMS with self-reported mild, moderate and severe disability (according to the EDSS) as well as between those who were fully ambulatory or ambulatory with assistance. They further demonstrated strong correlations between this variable and other patient reported outcome measures (including the MSWS-12). Interestingly, this study also found the same pattern of group differences and correlations in the SD (or to a lesser extent in 2 other measures of variability) of the total daily movements counts. The authors hypothesized that this observation supported the idea that gait descriptors variability was not only containing noise, but also relevant information that might be helpful to quantify neurological impairments. No hypotheses were advanced regarding the origin of this increased variability. It is noticeable that in another study investigating the association between energy cost of walking, objective gait parameters (gait speed, double limb support time and stride length) measured by a walking mat and daily physical activity quantified by an accelerometer over 7 days in pwMS mildly disabled (93), no significant association was found between these last two parameters (although this was not the primary aim of the study). Other authors found such association (136), using the 6- and the 2-minute walk tests to measure gait speed. Daily physical activity measured by accelerometers and walking speed over long distances association was stronger in pwMS with a disability considered here as moderate (EDSS 4.5-6.5). Thus there is conflicting evidence about the association of real-life ambulatory monitoring of walking capacities in pwMS with objective gait parameters measured in the controlled setting of a clinic or a gait laboratory. A possible explanation for this discrepant observation would be that the system with which gait descriptors are recorded yields different informations. While accelerometric techniques are probably the ideal tool to monitor real-life walking function, we believe that their lack of spatial resolution – at least when only one device is used – argues against their use for precise pathophysiological studies of walking impairment in MS.

### 4.1.3  Global positioning systems (GPS)

Creange et al used a global positioning system as an odometer in 31 pwMS (median EDSS 3.5, range: 1.5 – 6.5) to measure their walking capacities (94). The authors asked

subjects to walk « as usual » with the GPS and to interrupt it when they were not able to walk farther, considering the measured distance as the maximum objective walking distance. Moderate correlations were found between this parameter and the EDSS, the MSWS-12, the time to walk 10 m and the maximum subjective walking distance. The strongest correlation ($r^2$=0.75) was with the walking speed on a short distance (calculated from the time to walk 10 m). Interestingly, the maximum objective walking distance measured in pwMS with the same EDSS values varied considerably, e.g. between 500 and 3500 m for pwMS with an EDSS of 3.5. Across the range of measures obtained in the whole population, the highest maximum objective walking distance recorded was 4550 m, which corresponds to the 4000 m threshold we chose in previous works (126, 137) to distinguish fully ambulatory subjects from those with a limited walking capacity.

### 4.1.4  Three-dimensional gait analysis systems

A very high spatio-temporal resolution can be achieved for movement analysis through the use of three-dimensional analysis systems. In the field of MS-related gait impairment, very few studies have been performed with such motion capture systems. Remelius et al studied gait impairments in pwMS across fixed and preferred walking speed in a set-up consisting of a walking mat and 8 Oqus cameras (112). Each subject was wearing 50 reflective markers to track segmental kinematics. This allowed the measurement of double limb support time and stride width, which were increased in 19 pwMS (with mild to moderate neurological impairment) compared to healthy volunteers despite a comparable WS in the preferred pace type of walk. Moreover, an unstable balance in pwMS, but not in healthy subjects, was suggested by the dynamic between the centre of mass of the head, the whole body and the anterior boundary of the feet during gait.  In an other work using motion capture, Chee et al used a Vicon system as a gold standard to validate the capacity of an instrumented rollator to measure step width during the walk of pwMS in different environments (138). In other neurological diseases such as cerebellar ataxias, precise radio-clinical correlation have already been attained through a combined approach using MRI and motion capture systems (139), providing new insights into the neural basis of gait physiology. These highly precise tools are however expansive, and require a significant amount of time to

acquire data, making them unsuitable both for routine clinical use and for large scale multi-centre trials.

### 4.1.5 Relative contribution of the different dimensions of gait to its variance

Before moving to the description of our gait analysis system, it should first be stated that among the different work described above, most authors focused on the demonstration of specific anomalies of gait in pwMS, some of those conceptually related and others unrelated to walking speed. More precisely, the relationship between the measured gait features with walking speed or any other dimension of gait was not established. In most research performed, it was assumed based on clinical ground that specific gait features were representative of specific dimensions, e.g. step length for walking speed step width for ataxia (132). Despite some evidences favouring this type of approach, it should be kept in mind that no rigorous study confirmed the underlying assumption. Second, the relative importance of the different measured dimensions of gait relatively to its variance have not been established either. At present, it is thus unclear which of walking speed or ataxia (or any other dimension) is the main factor influenced by the impact of MS on gait.

## 4.2 Range laser scanners technology

### 4.2.1 Introduction and objectives

Taking into account advantages and limitations of existing technologies, current evidences they provide, and our need for further explanations regarding the mechanisms underlying gait impairments we observed in pwMS (especially their potential relationship to walking speed), we started to collaborate with the Intelsig group (Telecommunication and Imaging Laboratory, Montefiore Institute) from the University of Liège. Our objectives were:

1. To create a gait analysis system robust, easy-to-use and adapted to our needs and clinical environment
2. To develop clinically meaningful gait descriptors, taking into account walking speed but also unrelated dimensions of gait such as asymmetry and ataxia
3. To validate the measurement of these descriptors and explore their relevance in the context of MS

### 4.2.2 First objective: creating a new gait analysis system

**Publication #4:** Pierard S, Phan-Ba R, Droogenbroeck MV, Belachew S. A new low-cost and non-intrusive feet tracker. *Workshop on Circuits, Systems and Signal Processing (ProRISC).* 2011:382-7.

Our first objective was to design a new gait analysis system combining the following characteristics:

- Robust, rapid and easy-to-use in order to allow acquisition of data in the context of routine clinical practice or multicentre clinical trials
- Possibility to record gait descriptors sensitive to balance, asymmetry of leg function and spasticity, i.e. gait features that might not be captured by walking speed alone
- Spatio-temporal resolution as high as possible without compromising the 2 previous prerequisites

This work was achieved in collaboration with the Intelsig Lab through the use of range laser scanners technology (RLS, Figure 14)(140). RLS devices emit light in a plane within which they measure the distance of any object with spatial and temporal resolutions of ≈1 cm and 15 Hz, respectively. By using several RLS, we analyse an horizontal slice of the scene that is parallel to the ground, at a chosen height of 15 cm – just above the tibiotarsal joint in stance phase and below the theoretical maximum height reached by a



**Figure 12:** We use Range Laser Scanners (RLS, BEA LZR-i100, left) to produce a « curtain » horizontal and parallel to the ground, allowing the detection of feet position and their tracking as the subjects walks throughout the setting (right).

foot during the swing phase of a subject with a height ≈1.7 m. Using several RLS allows to cover a wider area and to reduce occlusions. In (140), we explain how it is possible

from this setting to calculate the position of an object (the feet) and hence its trajectory (feet paths during any type of walking task).

In brief, the rater chooses a path that is pre-encoded in the system and represented on the floor, and asks the subject to follow it. The system measures the positions of both feet, and their trajectories are obtained by mathematical transformation, guaranteeing that accelerations and velocities of the feet are continuous. At each instant, the person's location is determined as the midpoint between his/her feet. In such a way, an estimation of the person's trajectory is also obtained. Then, the three trajectories (left foot, right foot, and person) are registered with the path. The times $t_{start}$ and $t_{finish}$ at which the person crosses the starting and finishing lines are automatically derived from his registered trajectory. Only the data acquired during this temporal interval are further analysed. This methodology differs from stopwatch measurements where the leading foot is used to determine the crossing times.

### 4.2.3 Second objective: development of clinically meaningful gait descriptors

Our second objective is to design gait descriptors we consider pertinent from the clinical point of view. This result is obtained in two steps. First, we derive 3 signals from the trajectories. Next, the signals are summarized in 26 quantitative gait descriptors.

#### 4.2.3.1 Signals

The first signal extracted indicates *which foot is moving* at each instant: the left, the right, or none. Since the subject is considered as walking, the system assumes that it is not possible to have the two feet moving simultaneously. In practice, a foot is never at a standstill, even in stance phase. This is related to the fact that sensors observe a cross-section of the leg, and that minimal movements are always observed (e.g. trousers). In order to know if a foot is moving, we thus have to compare its velocity to a positive threshold here arbitrarily chosen to be the person's mean velocity, because the maximum feet velocity is guaranteed to be larger than the mean velocity.

The second signal extracted indicates the *cumulative distance* travelled by each foot since the instant at which the subject crosses the starting line. These signals relate to the so-called unregistered trajectories (i.e. the actual trajectories of the feet, not the one projected on the path).

The third signal concerns *instantaneous distances*:

      1. The interfeet distance is the distance between the two legs

2. The lateral distance is the length of the vector joining the two feet, projected on an axis perpendicular to the path

3. The deviation relates to the distance between the person's position and the followed path. It is computed as the distance between the corresponding points on his unregistered and registered trajectories.

4. The longitudinal signed distance has been created in order to detect gait asymmetry: it is positive if the right foot is in front of the left one, and negative otherwise. Its magnitude is computed as the length of the vector joining the two feet, projected on (an thus parallel to) the path.

### 4.2.3.2 Gait features

Using these four signals, the 26 following descriptive parameters of gait are measured:

1. $l_p$: length of the person's unregistered trajectory.

2. $l_l$: length of the left foot unregistered trajectory.

3. $l_r$: length of the right foot unregistered trajectory.

4. $l$: length of the segment that is analysed. Theoretically, it can be slightly shorter than the path's length because of the data acquisition frequency (currently 15 Hz). It is computed as the length of the person's registered trajectory.

5. $v_p$: mean velocity of the person, $v_p = l_p /(t_{finish} - t_{start})$

6. $v_l$: mean velocity of the left foot, $v_l = l_l /(t_{finish} - t_{start})$

7. $v_r$: mean velocity of the right foot, $v_r = l_r /(t_{finish} - t_{start})$

8. $v$: useful velocity, $v = l/(t_{finish} - t_{start})$. Thus, if the subject cuts the turns, $l > l_p$ and $v > v_p$, while if he deviates from the path and zigzags, $l < l_p$ and $v < v_p$. The velocity measured according to this modality is comparable to the walking speed measured with a stopwatch.

9. $V_l$: maximum velocity of the left foot. We compute the maximum velocity for each interval during which the left foot is detected moving (according to the first computed signal), and keep the median of these values (in order to filter out outliers).

10. $V_r$: maximum velocity of the right foot, computed analogously to $V_l$.

11. $d$: mean value of the inter-feet distance signal.

12. $d_\perp$: mean value of the lateral inter-feet distance.

13. $\Delta$: median gait cycle duration. The gait cycles are segmented with respect to both the left and the right foot. The limit of a gait cycle relative to a given foot is arbitrarily

defined as the mean time between the instants when the movement of this foot starts and finishes. $\Delta$ is defined as the median duration of all – left and right – extracted gait cycles.

14. $\Delta_l$: stride length of left foot. It is the median distance travelled by the left foot during a gait cycle.

15. $\Delta_r$: stride length of right foot, computed analogously to $\Delta_l$. It is possible that $\Delta_l \neq \Delta_r$ since we consider the unregistered trajectory, and not the registered version. For example, the travelled distance by the foot of a trailing, paretic limb might be longer if its circumduction is increased.

16. $\varphi$: left foot spatial lateness (or right foot advance) is the mean of the longitudinal signed distance signal. Besides the effects of the incomplete gait cycles present in the analysed interval, this measure might be helpful to quantify the degree of asymmetry of a gait where the trailing limb stops earlier than the normal one.

17. Proportion of the gait cycle time in double limb support. This descriptor corresponds to the proportion of time during which both feet speed is below $v_p$, and hence considered near 0.

18. Proportion of left foot moving time over the gait cycle. This descriptor is determined by the proportion of time during which the left foot is detected moving at a speed higher than the mean $v_p$.

19. Proportion of right foot moving time over the gait cycle, computed analogously to the previous descriptor.

20. Maximal deviation of the person: maximal value of the deviation signal (that is the distance between the person's position and the followed path).

21. Mean deviation of the person: mean value of the deviation signal.

22. RMS deviation. This is the root mean squared value of the deviation signal. This descriptor is less sensitive to outliers than the maximal deviation, but it penalizes more the large deviations than the mean deviation does.

23. $\sigma_l$: variability of the left foot strides. This is the SD of the length of the vector joining two consecutive support points for the left foot, projected on the path. This descriptor has been designed relatively to abnormalities which might especially be observed during the « heel-to-toe » type of walk (tandem gait), which has been shown to be more sensitive to cerebellar disturbances (141, 142). In a non-ataxic subject performing a tandem gait, the stride length is expected to be constant (with a minimal value imposed

by the feet size). Therefore, in this type of walk this descriptor should ideally be close to zero, and reflects the longitudinal imprecision of the foot placement when it increases. In « normal » types of walk (preferred pace or as fast as possible), it represents the variability of the step length.

24. $\sigma_r$: variability of the right foot strides (computed similarly to $\sigma_l$).

25. $e_l$: mean distance between the support points of the left foot and the path. When the subject is asked to adopt a tandem walk, this descriptor is also expected to be zero. Therefore, it reflects the imprecision of foot placement on an axis perpendicular to gait trajectory.

26. $e_r$: mean distance between the support points of the right foot and the path.

### 4.2.4 Third objective: clinical validation

#### 4.2.4.1 Introduction and objectives

Having created a new gait analysis system with 26 gait descriptors we subjectively considered as clinically meaningful, we have used several approaches to evaluate their soundness in clinical practice.

In the work described here, we retrospectively tested the ability of our gait analysis system to quantify gait characteristics of healthy subjects and pwMS, and explored the different components of gait highlighted with our technique. While several aspects of gait disorders related to MS can potentially be studied with our system, as a first step we aimed at defining the main factors underlying gait variance among a population of pwMS and healthy subjects, and draw hypotheses about which dimension of walk they represent based on the features we quantified. Next, we compared how these factors differed between pwMS with different disability levels and healthy subjects.

## 4.2.4.2  Methods

4.2.4.2.1   Walking paths, distances and type of walk

To attempt reproducing distances (and thus results) as comparable as possible to those already obtained in previous works a path of 25 feet and a path of 20 m were chosen.
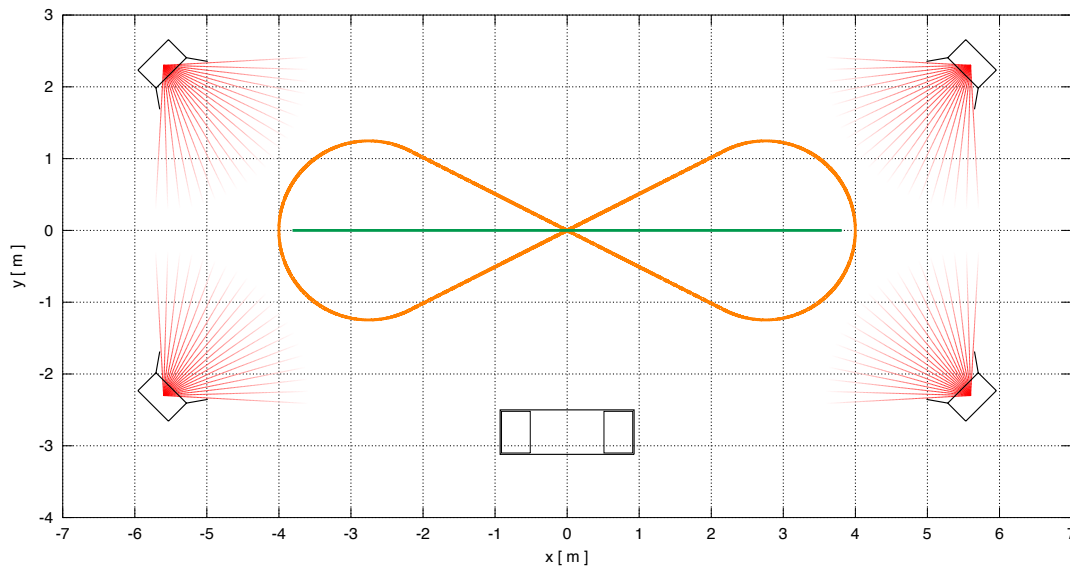


**Figure 13:** *Schematic view of the walk analysis zone.* Two paths are drawn on the ground, a straight line of 7.62 m (green) and a figure of eight pattern of 20 m (orange), surrounded by 4 RLS devices at each corners (red).

Those were distinctly represented on the ground (Figure 13). The 25 feet path was a straight line and the 20 m track followed a figure of eight pattern. The latter allowed the evaluation of longer distances of 100 or 500 m by asking participants to perform 5 or 25 laps, respectively. In these particular walk tasks, the alternative succession of right and left turns is supposed to prevent vestibular overstimulation and hence dizziness. In addition to the « as fast as possible » type of walk (AFAP), which is thought to represent the best performances a participant can achieve and was used in our previous protocols (and the MSFC guidelines), we also asked participants to walk in a comfortable type of walk (Preferred Pace, PrP) and heel-to-toe (tandem gait). The PrP type of walk has two advantages: (i) it is probably closer to the « real-life » type of walk, even though in this case the environment in which it is recorded is not and (ii) it is generally accepted that a slower walking speed is associated with an increased individual variability of gait descriptors (143, 144), which might be of interest for future analysis. The heel-to-toe

type of walk is a classic semiological approach in the clinical examination of gait function to detect subtle ataxia, and has been shown to be the only type of walk where gait abnormalities could be detected in subjects with mild cerebellar damage (141, 142). Participants were thus systematically asked to walk following this protocol:

1. 25 foot walk, preferred pace, two runs
2. 25 foot walk, as fast as possible pace, two runs
3. 25 foot walk, tandem gait, two runs
4. 20 m walk, preferred pace, one run
5. 20 m walk, as fast as possible pace, one run
6. 20 m walk, tandem gait, one run
7. 100 m walk, preferred pace, one run
8. 100 m walk, as fast as possible pace, one run
9. 500 m walk, as fast as possible pace, one run

Long distances (100 and 500 m) were performed at the end of the sequence in order to minimize (and investigate later) the impact of test-related fatigue. All participants were allowed to rest a few minutes between walk tests if they felt tired but were otherwise invited to continue walking with no more stops than mentioned above. The total walked distance was thus 805.72 m per trial.

Values of each 26 gait features obtained from the 25-foot walk, which was performed twice in each type of walk, were averaged as for the walking speed in the T25FW.

## 4.2.4.2.2 Population studied

Healthy subjects were recruited through local advertising. Each subject fulfilled a standardized medical questionnaire to ensure that no current or past disease (including drug or ethanol consumption) could interfere with the study procedure.

For all participants, collected demographics included age, sex, handedness, shoe-size, height and weight. For pwMS, disease duration, type of MS and EDSS score (with all functional subscores) were additionally collected. pwMS participating in gait analysis trials who had experienced a recent change in their EDSS (i.e. $\geq 1$ point in the global score or $\geq 2$ point in one subscore within the last 3 months) were excluded from the present analysis.

4.2.4.2.3 Statistical analysis

All observations were kept for the statistical analysis including those for which the whole set of gait descriptors was not available (e.g. pwMS unable to complete the entire testing session).

In order to exclude the effect of different metrics and to minimize errors related to non-normal distributions in our set of variables, all gait features values were standardized to a z-score (relative to the entire population).

For each walk test, a factorial analysis assessed data variance structure. The number of eigenvariates in the performance space that were retained for the analysis was set to account for 15% of data variance. A factorial load threshold of 0.6 was operationally used to consider significant the weight of a gait feature to a given eigenvariate.

In order to outline the importance of subject-related factors accounting for the variance of gait, a second factorial analysis was performed for each walk test after transposition of the data set (i.e. gait features x observations).

Eigenvariates in the participant space were retained as dependent variables in a mixed model analyses. These mixed effect statistical analyses were conducted, in participant space, with distance (T25FW, T20MW, T100MW or T500MW) and instruction (Preferred pace, As fast as possible or Tandem) as fixed effects and group allocation as a random factor (considering either the entire MS population or only pwMS with a low EDSS) or the disability status (as quantified by the EDSS, only in pwMS).

All statistical tests were applied with a two-tailed analysis and 0.05 as a level of significance and were performed using Statistica, version 10 for Windows, Statsoft Inc., France.

## 4.2.4.3 Results

4.2.4.3.1 Population characteristics

Sixty-nine pwMS and 37 healthy volunteers participated in the study. Their demographics are displayed in Table XI. No baseline characteristic differed significantly between the two populations, except from the age that was higher in the pwMS population and the gender with a predominance of female in pwMS and a predominance of male in controls.

**Table XI:** Baseline demographics of pwMS and control subjects studied with RLS

|  | pwMS | Controls |
|---|---|---|
| Number | 69 | 37 |
| Gender (% female) | 63.8 | 45.9 |
| Age (median, range, years) | 43, 20-69 | 28, 22-63 |
| Body Mass Index (mean ± SD, kg/m$^2$) | 23.44 ± 3.62 | 23.98 ± 3.92 |
| EDSS (median, range) | 4.0, 0-5.5 | n.a. |
|     0-2.5 (number of subjects, %) | 18 (26) | n.a. |
|     3.0-3.5 (number of subjects, %) | 14 (20.2) | n.a. |
|     4.0 (number of subjects, %) | 27 (39.1) | n.a. |
|     4.5-5.5 (number of subjects, %) | 10 (14.5) | n.a. |
| MS type (CIS/RR/SP/PP, %)[1] | 20.3/55.1/10.1/14.5 | n.a. |
| Disease duration (mean ± SD, range, years) | 12.1 ± 10.1, 0 - 42 | n.a. |

1: CIS, Clinically Isolated Syndrome; RR, Relapsing-Remitting; SP, Secondary Progressive; PP, Primary Progressive.

#### 4.2.4.3.2 Contribution of the different gait descriptors to gait variance

Figures 14 and 15 depict the results of the factorial analysis performed on the entire population (healthy volunteers and all pwMS, regardless of their disease type or disability scores). In order to account for at least 15% of data variance in each test, we kept the first 3 eigenvariates. The corresponding eigenvalues (i.e. the proportion of variance across the 26 gait features explained by each factor) are displayed for the 9 walk tests in the variable space in Figure 14 and in the participant space in Figure 16. Figure 15 illustrates the distribution of eigenvariate's load across the 26 features for the T25FW (in AFAP and in tandem gait) and for the T20MW in tandem gait (rows) and eigenvariate (columns). The T25FW, the T20MW, the T100MW in PrP and AFAP and the T500MW in AFAP all displayed a similar distribution of eigenvariate's load across the gait features.

The prominent gait features (highlighted in red in Figure 15) consistently participating to the first eigenvariate in most tests were the mean velocity of the person, the mean and maximum velocity of the left and right foot, the useful velocity, the proportion of left and right foot moving time over the gait cycle and the double limb support time. However, the T20MW performed in tandem gait displayed a different factorial profile:

prominent loads were observed for the total distance travelled by the person, by the left and right foot, the useful velocity, the maximal, mean and RMS deviation from the trajectory, the left foot lateness, the variability of the left and right foot strides and the mean distance between the support points of the left or right foot with the path. Consequently, we considered that the first eigenvariate mostly conveyed information about gait speed, except for the T20MW (see discussion).

For the second and the third eigenvariates, at least one out of the 3 gait features related to the deviation of the person from the path (mean, maximal or RMS), the variability of the left or right foot strides, the mean lateral inter-foot distance (for the test performed in PrP) and the mean distance between the support points of the left or right foot with the path were considered to participate significantly (highlighted in green and brown, respectively, Fig 15).

Again, T20MW differed from other tests by prominent gait features participating significantly to its $2^{nd}$ and $3^{rd}$ eigenvalues that largely overlapped with those participating to the $1^{st}$ eigenvalue of the 8 other walk tests, i.e. the mean velocity of the person, of the left foot, the maximum velocity of the left and right foot as well as their proportion of time moving over the gait cycle.

Finally, participation of the gait features related to the travelled distance (total or useful distance travelled by the person, by the left or right foot) were seen inconsistently across the 3 eigenvalues.
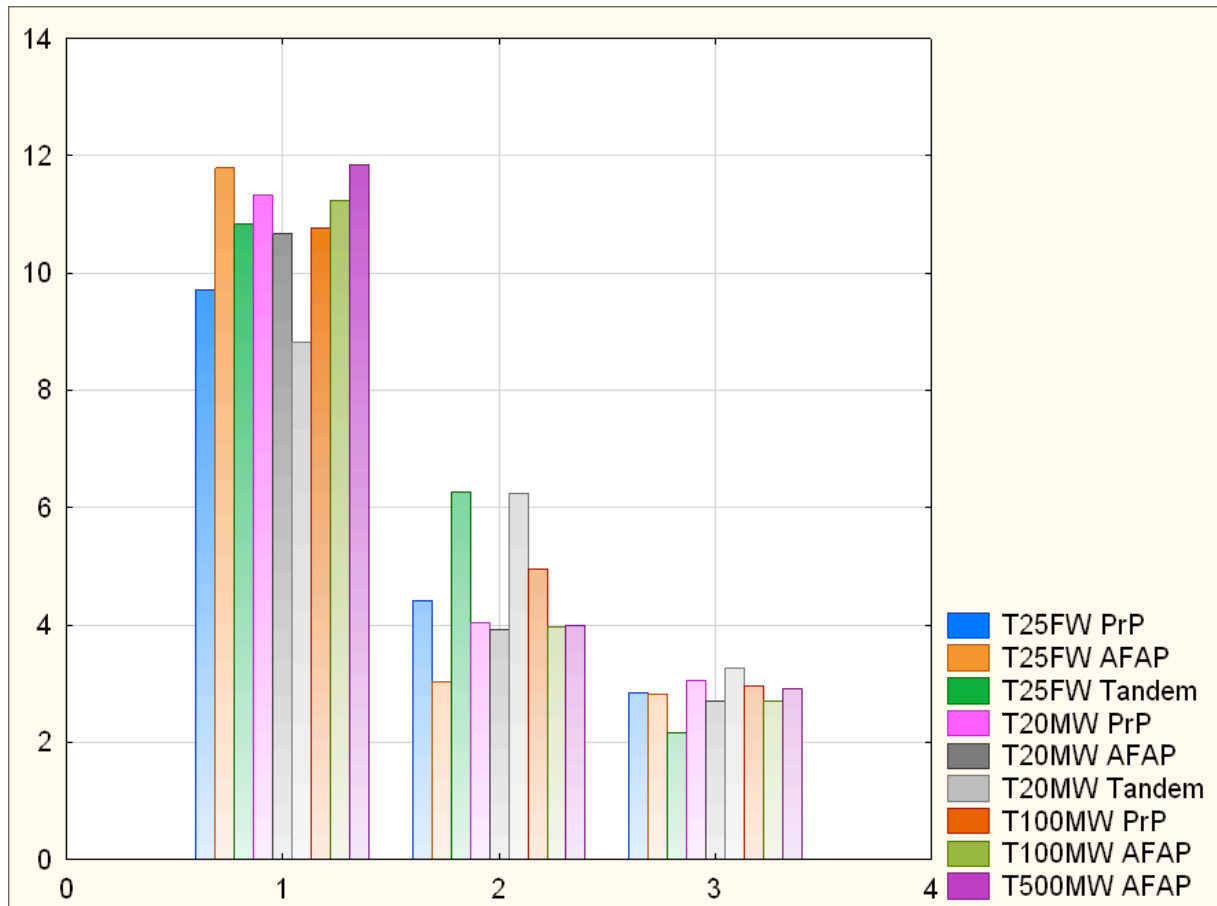
**Figure 14**: Proportion of variance of gait explained by the first 3 eigenvariates in the performance space, derived from the 26 gait features, in the 9 walk tests.

**Figure 15:** Relative contribution of the 26 gait features to the 3 first eigenvalues in the 9 walk tests. Gait features are numbered according to the list in "6.2.3.2" and those with a factorial load above 0.6 are highlighted in red (first eigenvalue), green (second eigenvalue) or brown (third eigenvalue). The 6 walk tests non displayed (the T25FW in PrP, the T20MW and the T100MW in PrP and AFAP and the T500MW in AFAP) all followed the same pattern of gait feature factorial load as the T25FW in AFAP.
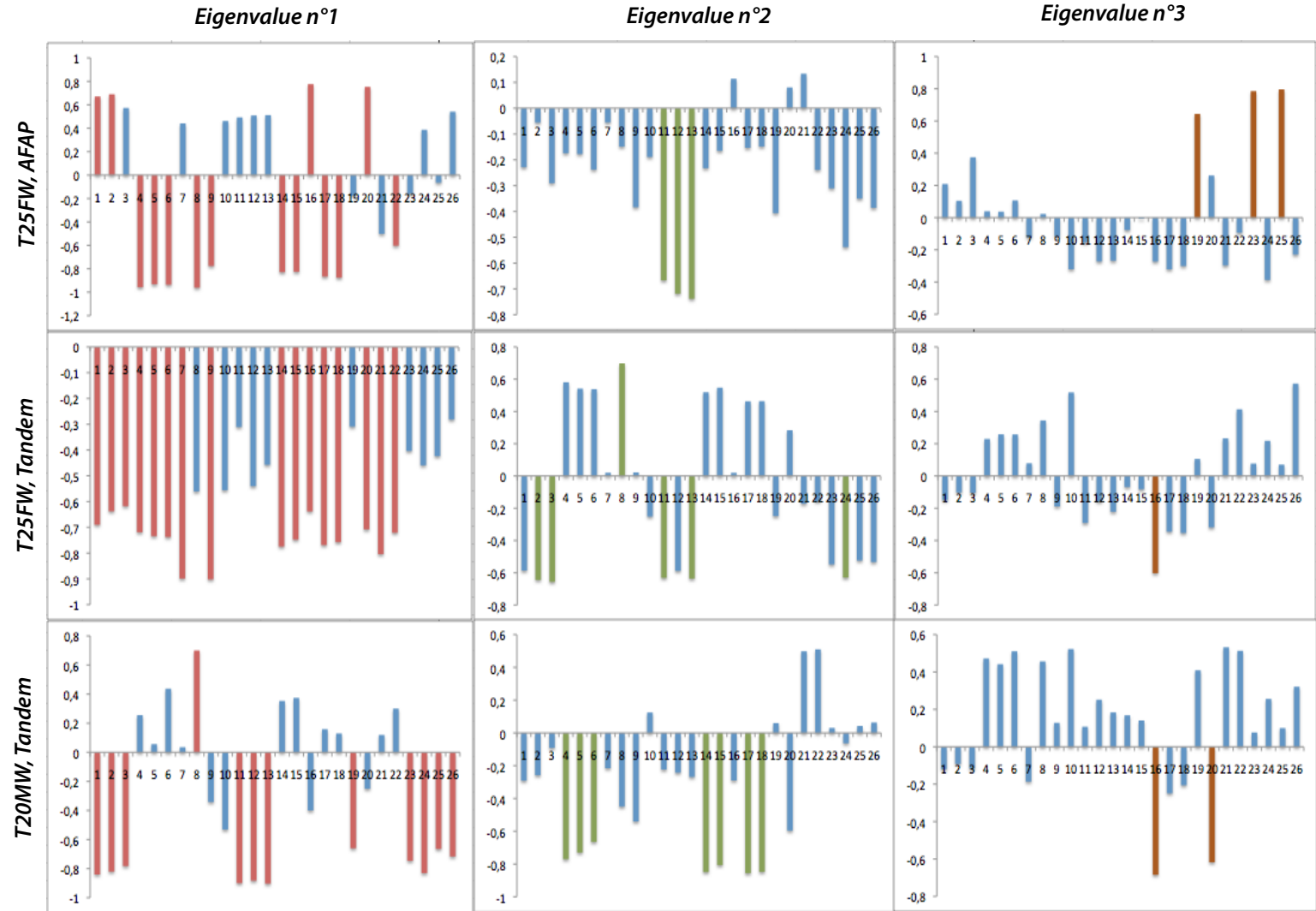
Variance partitioning between pwMS and healthy volunteers

The eigenvariates obtained from the factorial analysis performed on the transposed data set are displayed in Figure 18.
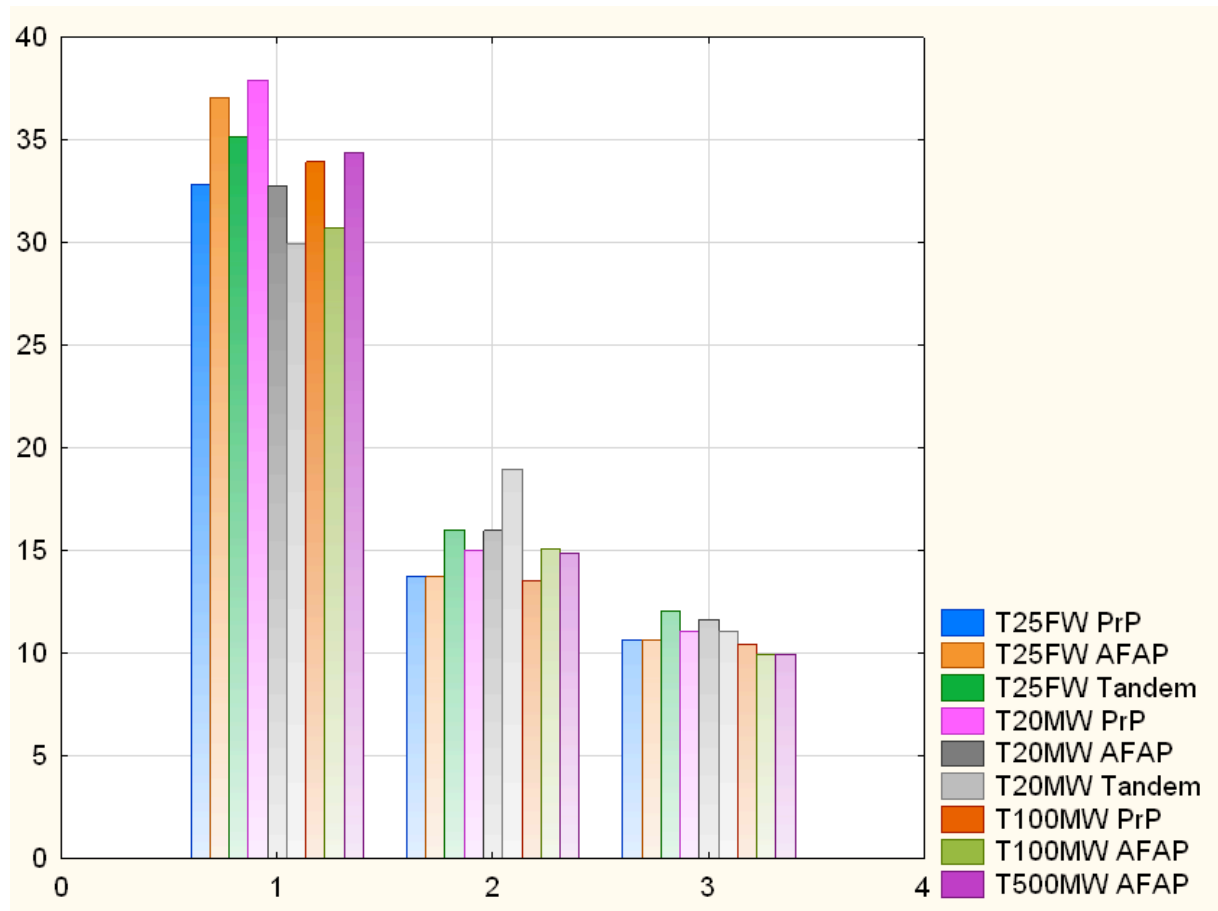


**Figure 16:** Three first eigenvalues obtained from the factorial analysis of the transposed matrix of data. The variance explained by the eigenvalues is in the participant space, hence related to inter-subjects differences.

Variance partitioning (VP) of the factorial load of pwMS and healthy subjects for the first eigenvariate found a significant effect for the group (F=42.296, df=1, p=0.02043, Figure 17A) and a significant interaction between the group and the instruction (F=11.704, df=2, p=0.03783, Figure 17B). VP of the factorial load of this population for the second and third eigenvalues found a significant interaction between the group, the walk test and the instruction (F=6.2702, df=3, p<0.001 and F=5.0574, df=3, p=0.001774, respectively, Figure 17C).
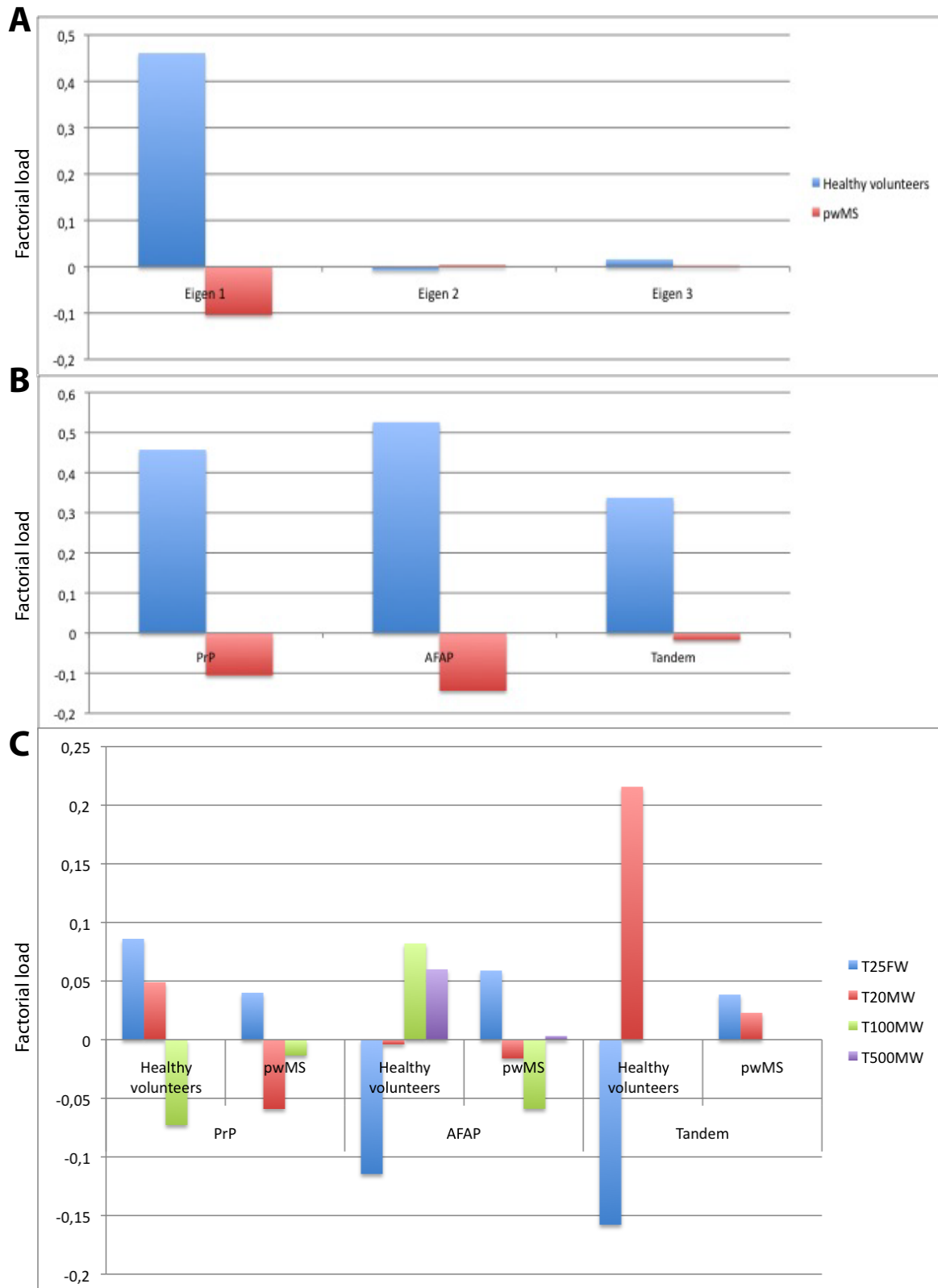
**Figure 17:** Significant interaction retrieved after variance partioning of the factorial load in the entire population (pwMS and healthy volunteers). For the first eigenvalue, we found a significant effect of the group (Panel A) as well as a significant interaction between the group and the instruction (Panel B). For the second and third eigenvalue (only the latter being shown in Panel C), a significant interaction was found between the group, the instruction and the distance.

VP of the factorial load of pwMS with a low EDSS (i.e. ≤ 2.5) and healthy subjects found a significant interaction between the group, the walk test and the instruction for the second eigenvalue (F=4.05088, df=3, p=0.004, Figure 18), with no other significant interaction in other any of the 3 eigenvalues.
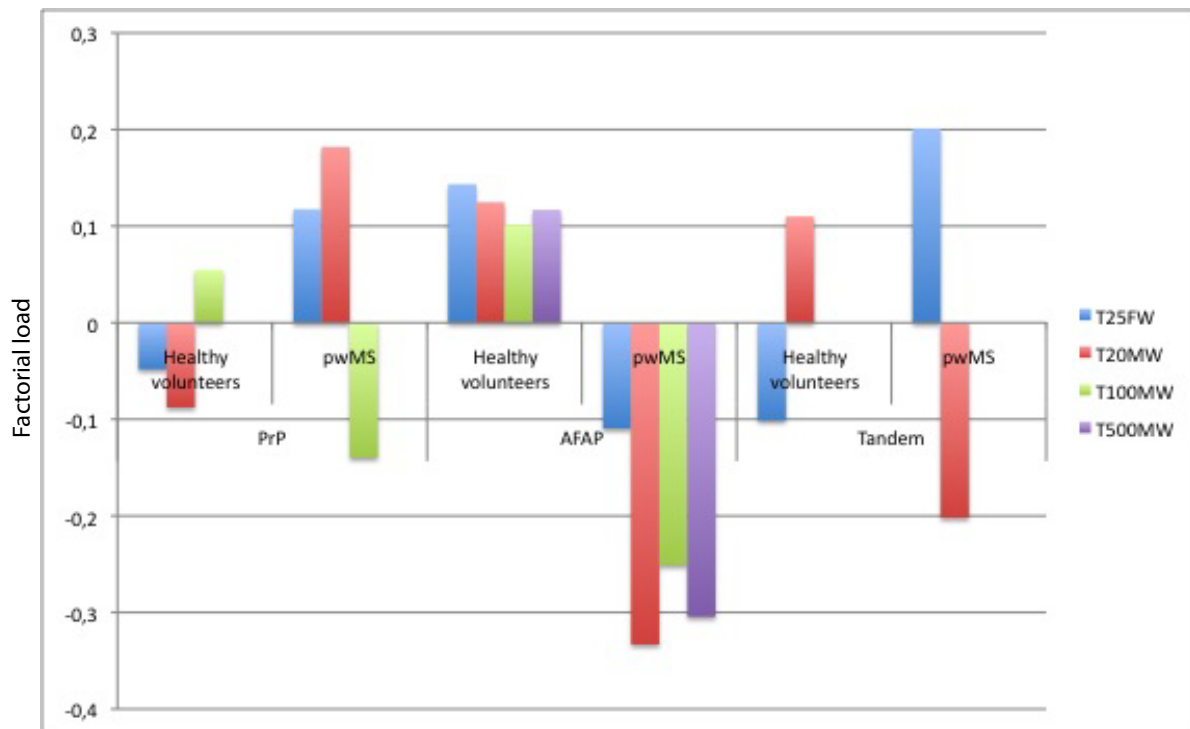


**Figure 18:** Variance partioning of healthy volunteers and pwMS with a low EDSS factorial load for the second eigenvalue showing a significant interaction between group, instruction and distance.

Finally, VP of the factorial load of pwMS stratified according to their EDSS as mild (0-2.5), mid-range (3.0-3.5) or high (4.0-5.5) showed a significant interaction between the group, the walk test and the instruction for the first and the second eigenvalues (F = 2.5714, df = 6, p = 0.0183 and F = 7.0392, df = 6, p < 0.001, respectively, Figure 19A and B), with no other significant results.
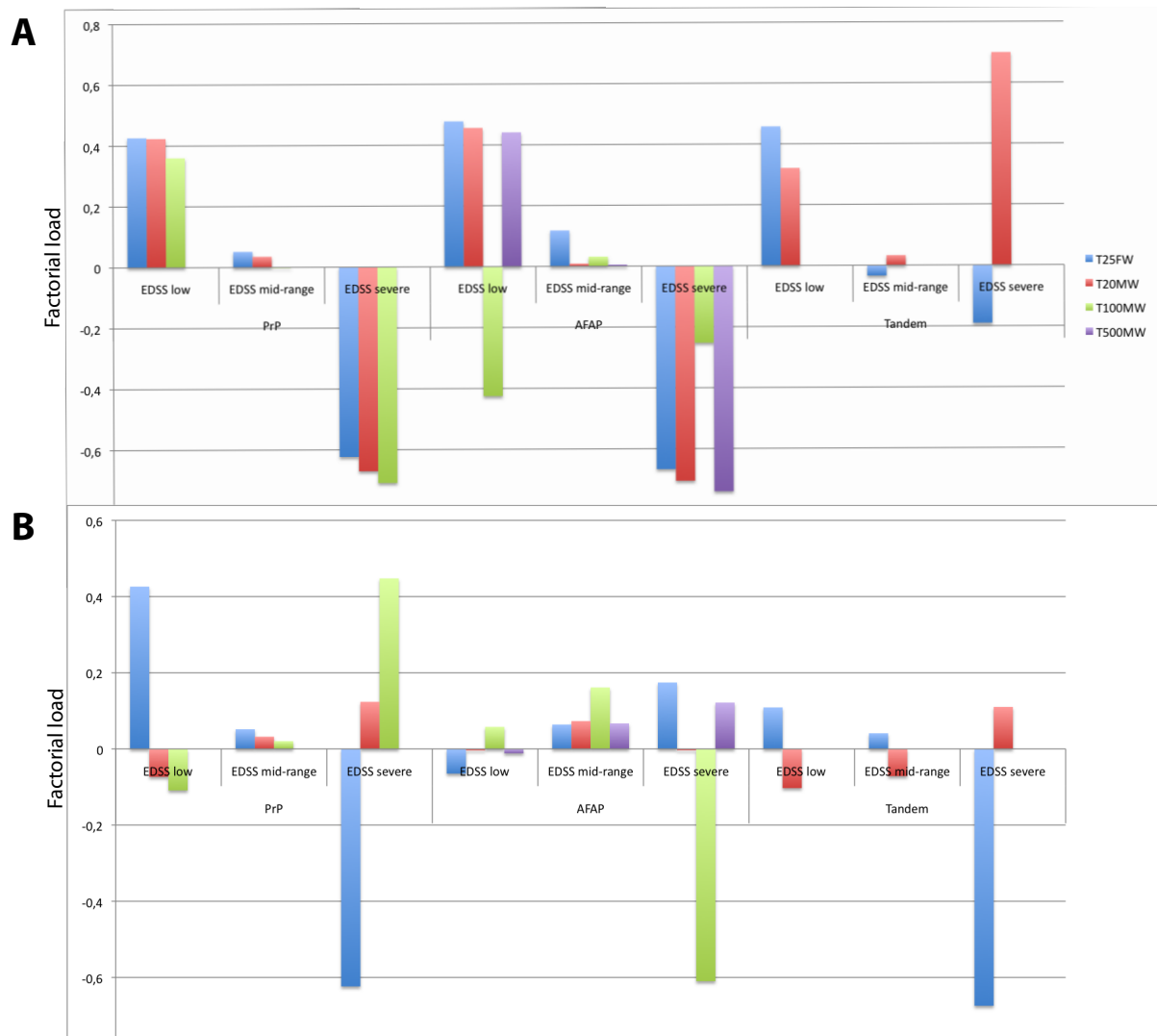
**Figure 19:** Variance partioning of pwMS (stratified according to their EDSS) factorial load for the first (Panel A) and the second (Panel B) eigenvalue, showing a significant interaction between group, instruction and distance.

### 4.2.4.4 Discussion

The present work was aimed at studying the results obtained from walk tests acquisitions performed with a new gait analysis system on a population of healthy subjects and pwMS with a broad interval of disability. Our objectives were to characterize the variance of gait according to the 26 gait descriptors we designed, and to evaluate the extent to which this variance was explained by the MS status and MS related disability.

The first factorial analysis performed allowed to ponder the contribution of the 26 predetermined gait descriptors by summarising their factorial load into 3 main eigenvariates explaining at least 15% variance of gait at the level of the entire population (healthy subjects and pwMS). These eigenvariates allowed us to reduce the dimension of the data set while taking into account colinearities between original

variables. However, it should be kept in mind that these factors together explained generally less than 20% of the total variance observed.

Individual examination of gait descriptors contributing significantly to the first eigenvalue in most walk tests (excluding the T20MW performed in tandem gait) showed that the main factor underlying gait variance was mainly constituted of features conceptually related to walking speed (person's mean velocity, individual foot mean or maximal velocity, useful velocity, proportion of left and right foot moving time over the gait cycle and double limb support time). This observation confirms that walking speed is the dominating feature to characterize gait. However, it is remarkable that about 85% variance is not explained by the first 3 eigenvariates, suggesting that other experimental factors participate in data variance, although not in a substantial and identifiable way.

In our view, the different pattern of gait features contributing to the first eigenvalue calculated from the T20MW performed in tandem gait (the total distance travelled by the person, by the left and right foot, the useful velocity, the maximal, mean and RMS deviation from the trajectory, the variability of the left and right foot strides and the mean distance between the support points of the left or right foot with the path) suggests that most of these are related to balance. Alternatively, one might also argue that those variables conveys (or interacts with) speed information.

When examining gait features which contributed significantly to the 2nd or the 3rd eigenvalues in the different walk tests performed in PrP or AFAP types, we recognize parameters related to the deviation of the participant's walk (mean, RMS or maximum value), the mean lateral interfeet distance, variability of the left and right foot strides and mean distance between the left foot and the path. Again, these features were all created in order to reflect the balance ability component of the person's gait. From these observations we can conclude that while balance is an important component of gait, it is not the dominant one, appearing after walking speed when studying their contribution to gait variance in a population of pwMS and healthy subjects.

The second factorial analysis performed the participant space of our dataset yielded eigenvalues that were related to the variability of gait features between each subject of our population.

It should be emphasized that neither eigenvalues nor factorial loads from the first and the second factorial analysis are strictly comparable: while the first analysis aimed at studying the contribution of the 26 gait features to gait variance measured over the

entire population, in order to outline its underlying main factors, the second aimed at measuring each individual subject's contribution to this variance. However, although the exact composition of the eigenvalues yielded by both factorial analyses cannot be superposed, it should be noted that it differed little, suggesting that the assumptions advanced on the basis of the first analysis could be applied to the second.

In the mixed effect analysis, demonstration of a significant effect of the MS status alone on the 1st eigenvalue confirmed that walking speed explain most of MS-induced walking impairment. Interestingly, the significant interaction between the group and the instruction (i.e. type of walk) indirectly confirmed our previous observation of a differential effect on walking speed of the instruction between pwMS and healthy subjects, although here additionally to PrP and AFAP the tandem walk was also taken into account. The hypotheses attempting to explain the differential effect of PrP vs. AFAP according to the MS or healthy status are discussed elsewhere (see 5.3).

It is also noteworthy that while no significant effect was found on the first eigenvalue between pwMS with a low EDSS and healthy volunteers, a significant interaction between test, instruction and MS status was observed for the second eigenvalue, suggesting the previously described presence of a subtle ataxic component in the gait of pwMS with no apparent disability and no change in their walking speed.

The same interaction was revealed by comparison of healthy subjects with the whole pwMS population (where it was also present for the third eigenvalue), and when comparing pwMS between them. This also suggests that loss of balance induced by MS was detected, and that its variation with the disability status differed significantly across our pwMS group.

Several shortcomings of our study deserve further qualification.

First, the most important limitation is validity. Although the system is physically accurate (spatio-temporal resolution of 10 mm and 15 Hz, respectively), we did not compared it to another validated gait analysis system. However, we argue that signals and gait features measured with our system cannot be recorded with other technologies, except perhaps three-dimensional gait analysis systems, which makes the use of a « true ground » difficult. This lack of gold standard led us to use factorial analysis and variance partitioning analysis as a first approach to indirectly evaluate the clinical relevance of our measures. In addition, multivariate analyses are being developed with the same objective. Similarly, a strict comparison between the timed values obtained on walk

tests performed on the figure of eight trajectory (the T20MW, the T100MW and the T500MW) is not possible because in the original walk tests we did not ask our subjects to follow this type of path.

Second, at present, we have not yet collected enough data to allow a clear statement about the reproducibility of our measures, although first data look positive.

Third, for every significant effect demonstrated in the mixed model analysis, we were not able to finely interpret the meaning of the observed group differences, because no post-hoc analysis was performed. This issue will be addressed in future work.

Finally, the length and duration of the acquisition protocol are other significant limitations (with a distance of 805.72 m and approximately 10 minutes per subject per trial). Nevertheless, this was deliberately chosen in order to allow further analysis that will help us to define which walk test to administrate when looking for a specific dimension of gait alteration in pwMS (i.e. the T20MW performed in tandem gait seems particularly sensitive to ataxia based on the results of the first analysis, although this should be demonstrated on an independent cohort of ataxic subjects). This lengthy protocol may have induced motor fatigue in every subject tested, especially in the longer distance walk tests (T100MW and T500MW) that were performed at the end of the sequence. Although this bias was probably minimised by the administration of the walk tests in a systematic order, it will have to be taken into account for future comparisons. It may theoretically have been circumvented by random administration of walk tests, but we considered the number of acquisitions necessary to apply such a methodology too high. Only few pwMS with a so-called high disability status (EDSS > 4.0, n = 10) were able to fulfil the walk tests because of the length of the protocol, which makes analysis of this particular subgroup of subject impossible for statistical reasons. The same apply to the pwMS with a progressive disease. At present, we cannot state upon the usefulness of the T100MW and the T500MW in our cohort, because a specific analysis of distance induced locomotor fatigability has not been performed.

### 4.2.4.5 Conclusion and perspectives

The second part of our work aimed at improving the evaluation of gait disorders in persons with MS by developing and validating a new gait analysis system.

We achieved the development of a system easy to implement in clinical routine, with rapid acquisitions – although the set of walk tests to perform has yet to be precisely

defined and reduced accordingly – and a high number of gait features that may ultimately be modified or selected in order to fit to the type of gait disorder presented by the subject. The continuous monitoring of gait features according to feet paths along the walk tasks probably allow a better delineation of subtle gait abnormalities that may otherwise remain unrecognised by conventional gait analysis methods. We here confirm that although walking speed is clearly the main component influencing gait variance across healthy subjects and pwMS, there are other factors coming into play, which seem to be independent of WS but more related to balance. As a first step in the validation process, we here provide indirect evidence that our technology is capable to distinguish the effect of MS (and its related disability) through gait analysis.

Future work should be focused (i) on the evaluation of the same set of gait features on an independent cohort of subjects in order to validate the present findings, (ii) on the study of their modifications along long distance walking tests that may be related to motor fatigue, (iii) on reassessment of healthy controls and pwMS over time to determine the reproducibility of our measures and their sensitivity to change in case of underlying neurological modifications (either degradation because of relapses or disease progression, or improvement due to therapy) and (iv) on multivariate analyses in order to uncover interactions between the different component of gait our technique can highlight. As a longer-term objective, the characterization of subtle gait feature modification that may be predictive of future neurological modification, especially in the progressive MS population, is a major goal. The implementation of new gait features that would be more sensitive to gait asymmetry (i.e. detection of a trailing limb) will be helpful for the monitoring of spastic gait, and the development of features focused on gait variability will provide insights into the mechanisms and kinetics underlying pathologic motoric output variability in CNS lesions.

Finally, the implementation of additional gait analysis methods such as accelerometry to our technique seems rationale in order to capture other features of walking ability (i.e. global mobility) and will help to pave the ground for the design of a truly multimodal characterization and monitoring pwMS mobility.

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# 6 List of abbreviations

| | |
|---|---|
| AFAP | As fast as possible |
| ARR | Annualized relapse rate |
| CIS | Clinically isolated syndrome |
| CV | Coefficient of variation |
| DI | Deceleration index |
| EDSS | Expanded disability status score |
| FS | Functional system (in the EDSS) |
| HV | Healthy volunteers |
| ICC | Intraclass correlation coefficient |
| MrWD | Maximum reported walking distance |
| MS | Multiple sclerosis |
| MSFC | Multiple sclerosis functional composite |
| MSWS-12 | Multiple sclerosis walking scale |
| PASAT | Paced serial addition test |
| PP | Primary progressive |
| PRO | Patient reported outcome |
| PrP | Preferred pace |
| pwMS | Persons with multiple sclerosis |
| RLS | Range laser scanners |
| RMS | Root mean square |
| ROC | Receiver operator characteristic |
| RR | Relapsing remitting |
| SP | Secondary progressive |
| T25FW | Timed 25-foot walk test |
| T25FW+ | Timed 25-foot walk test with a propelled start |
| T100MW | Timed 100-meter walk test |
| T500MW | Timed 500-meter walk test |
| VP | Variance partioning |
| WS | Walking speed |

# 7  Appendix

## 7.1   Supplementary material

## 7.1.1  The EDSS

| | |
|---|---|
| 0 | Normal neurological examination (all functional scores = 0) |
| 1 | No disability, minimal signs in one FS (one FS = 1) |
| 1.5 | No disability, minimal signs in more than one FS (more than one FS = 1) |
| 2.0 | Minimal disability in one FS (one FS = 2; others ≤ 1) |
| 2.5 | Minimal disability in two FS (two FS = 2; others ≤ 1) |
| 3.0 | Moderate disability in one FS (one FS = 3; others ≤ 1) or mild disability in three or four FS (three or four FS = 2; others ≤ 1); though fully ambulatory |
| 3.5 | Moderate disability in one FS with mild disability in one or two FS and other FS normal or not disabling (one FS = 3; one or two FS = 2; others ≤ 1); though fully ambulatory |
| 4.0 | Severe disability in one FS and other FS normal or not disabling (one FS = 4; other ≤ 1) or combination of lesser grades exceeding limits of previous steps; ambulatory without aid or rest ≥ 500 m |
| 4.5 | Ambulatory without aid or rest for ≥ 300 m; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps |
| 5.0 | Ambulatory without aid or rest for 3200 m (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5) |
| 5.5 | Ambulatory without aid or rest 3100 m |
| 6.0 | Unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting |
| 6.5 | Constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting |
| 7.0 | Unable to walk 5 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 h a day |
| 7.5 | Unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self |
| 8.0 | Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms |
| 8.5 | Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions |
| 9.0 | Helpless bed patient; can communicate and eat |
| 9.5 | Totally helpless bed patient; unable to communicate effectively or eat/swallow |
| 10.0 | Death attributed to MS |

Adapted from (70)

## 7.2 Publications

**7.2.1   Publication #1:** <u>Phan-Ba R</u>, Pace A, Calay P, Grodent P, Douchamps F, Hyde R, Hotermans C, Delvaux V, Hansen I, Moonen G, Belachew S. Comparison of the timed 25-foot and the 100-meter walk as performance measures in multiple sclerosis. *Neurorehabil Neural Repair*. 2011;25(7):672-9.

# Comparison of the Timed 25-Foot and the 100-Meter Walk as Performance Measures in Multiple Sclerosis

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## Abstract

*Background.* Ambulation impairment is a major component of physical disability in multiple sclerosis (MS) and a major target of rehabilitation programs. Outcome measures commonly used to evaluate walking capacities suffer from several limitations. *Objectives.* To define and validate a new test that would overcome the limitations of current gait evaluations in MS and ultimately better correlate with the maximum walking distance (MWD). *Methods.* The authors developed the Timed 100-Meter Walk Test (T100MW), which was compared with the Timed 25-Foot Walk Test (T25FW). For the T100MW, the subject is invited to walk 100 m as fast as he/she can. In MS patients and healthy control volunteers, the authors measured the test–retest and interrater intraclass correlation coefficient. Spearman rank correlations were obtained between the T25FW, the T100MW, the Expanded Disability Status Scale (EDSS), and the MWD. The coefficient of variation, Bland–Altman plots, the coefficient of determination, and the area under the receiver operator characteristic curve were measured. The mean walking speed (MWS) was compared between the 2 tests. *Results.* A total of 141 MS patients and 104 healthy control volunteers were assessed. Minor differences favoring the T100MW over the T25FW were observed. Interestingly, the authors demonstrated a paradoxically higher MWS on a long (T100MW) rather than on a short distance walk test (T25FW). *Conclusion.* The T25FW and T100MW displayed subtle differences of reproducibility, variability, and correlation with MWD favoring the T100MW. The maximum walking speed of MS patients may be poorly estimated by the T25FW since MS patients were shown to walk faster over a longer distance.

## Keywords

multiple sclerosis, ambulation/walking, outcome measurement, disability progression, EDSS

## Introduction

Although all neurological deficits caused by multiple sclerosis (MS) contribute to a patient's overall disability, ambulation is recognized as a key factor in determining a patient's functional status.[1]

In therapeutic and rehabilitation clinical trials, the Expanded Disability Status Scale (EDSS)[2] and the Multiple Sclerosis Functional Composite (MSFC)[3] score are the most widely used conventional scores for the quantitative assessment of the impact of MS on neurological status. In the EDSS, ambulation is evaluated through patients' recall of their maximum walking distance (MWD) and by the observation of the gait disturbances. The MSFC is a composite score that was developed in response to the lack of sensitivity and reliability of the EDSS. It is composed of 3 ratio-interval scales of neurological functions: the 3-Second Paced Auditory Serial Addition Test for cognitive function, the 9-Hole Peg Test for upper limb function, and the Timed 25-Foot Walk Test (T25FW) for the evaluation of leg function/ambulation.

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Specific therapies targeting ambulation dysfunction are currently emerging,[4] and gait evaluations are increasingly recognized as primary outcome measures in clinical trials and rehabilitation programs, especially in progressive forms of MS. In this context, the T25FW is by far the most widely used ambulation test. However, even though excellent inter-rater and intrarater reliabilities have been reported for the MSFC as a composite score, the T25FW component can display variable results,[5,6] especially in more disabled patients with slower walking speeds. This has been attributed to practice effect, test-related fatigue, and motivational issues.[7] In addition, the T25FW has been described as being hampered by low responsiveness and marked floor and ceiling effects,[8] mainly because it is assumed to reflect only speed over a short distance. Ambulation fatigue,[9] spasticity, coordination, and balance are not specifically assessed by the T25FW, which is why more refined gait evaluations have been proposed.[8]

To study ambulation characteristics of MS patients on a longer distance and to overcome the limitations of the T25FW, we evaluated the Timed 100-Meter Walk Test (T100MW). In MS, 100-, 200-, 300-, and 500-m distances represent the ambulation range of EDSS milestones 5.5, 5.0, 4.5, and 4.0, respectively. We chose the 100-m distance as the threshold in the EDSS beyond which patients require at least unilateral assistances.

## Methods

A total of 141 patients with a diagnosis of relapsing–remitting or progressive MS according to the Poser[10] and McDonald[11] criteria and 104 age- and sex-matched healthy volunteers used as a control group were enrolled in the study.

Both MS patients and controls performed the T25FW and the T100MW. The procedures were approved by the local ethics committee of the Medical Faculty of Liège. All the assessments were made by a certified MS nurse (PC) or by a physical therapist in charge of patients' rehabilitation programs (PG). All EDSS score were collected by a certified EDSS rater (RP or SB).

The MWD was evaluated as follows: control healthy volunteers all reported a MWD superior to 4000 m, which was considered as "unlimited." MS patients were asked whether they had the feeling that during the past 4 weeks their average walking performance had been unlimited and whether they thought they could walk for more than 4000 m without aid or rest. If so, they were considered to have an "unlimited" MWD. Patients considering themselves unable to walk more than 4000 m were defined as having a "limited" ambulation and were asked to evaluate as accurately as possible their MWD, that is, the maximum distance they thought they could walk without aid or rest, with a high risk of falling if they went on for a few meters more. Patients who evaluated their MWD as being less than 2000 m were considered to be patients with so-called restricted ambulation. The accurate MWD was measured for patients reporting to be unable to walk more than 500 m.

The T25FW was performed according to the published standardized instructions.[2,6]

For the T100MW, a 25-m walk (to be performed 4 times with 3 U-turns) was accurately measured in a corridor of at least 3 m width, devoid of obstacles. Running was prohibited. Patients could use assistive devices if absolutely necessary to perform the test. Ankle–foot orthosis was permitted if worn from onset for all evaluations throughout the trial. The subject was directed to the end of a clearly marked 25-m course (clearly defined on the floor) and instructed to stand just behind the starting line. We pointed out where the 25-m course ended and then instructed the patient as follows: "I'd like you to walk this 25-meter distance 4 times as quickly as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go." Timing started when the lead foot crossed the starting line. The examiner could not walk along with the patient as he/she completed the task. Timing was stopped when the lead foot crossed the finish line ($4 \times 25$ m). The examiner then recorded the subject's walking time to within 0.1 second, rounding up or down as necessary. We rounded up to the next tenth if the hundredth of a second's place was $\geq$.05, rounded down if the hundredth of a second's place was <.05 (eg, 55.45″ would round up to 55.5″ but 55.44″ would round down to 55.4″). On the day of the clinical evaluations, rehabilitation sessions or other demanding physical activities did not take place prior to the testing. The 2 sessions of the T25FW were always performed prior to the T100MW. Control healthy volunteers performed the T25FW and the T100MW twice to establish the test–retest intraclass correlation coefficient (ICC).

To evaluate the interrater reliability of the tests, 50 healthy volunteers and 40 MS patients underwent a second evaluation for the T100MW and the T25FW by another rater after a 15-minute resting time.

The mean walking speed (MWS) expressed in meters per second for both tests were obviously calculated by dividing 100 m by the time to perform the T100MW and 7.62 m by the time to perform the T25FW.

A Wilcoxon rank sum test was performed to compare walking test scores in healthy controls and MS patients. Test–retest and interrater reliabilities were evaluated using ICC.[12] The coefficient of variation (standard deviation divided by mean, expressed as a percentage) was used to compare relative variation between the 2 walking tests overall, by limited/restricted ambulation, and within each step of EDSS. The results from the 2 methods were also compared in accordance with the principles described by Altman and Bland.[13] Spearman rank analyses were used to assess the strength of the correlation between walking tests, EDSS, and MWD, and the coefficient of determination was obtained from a linear regression excluding outliers. The area under the receiver operator characteristic (ROC) curve provided an overall measure of the accuracy of each walking test in predicting limited ambulation. Last, a *t* test was used for between-groups comparisons, whereas a paired *t* test was used for within-group comparisons of the MWS on the T100MW with the MWS on the T25FW.

**Table 1.** Characteristics of Patients and Control Subjects

|  | MS Patients | Healthy Controls |
| --- | --- | --- |
| Number of patients/controls | 141 | 104 |
| Gender, % female | 68.8 | 63.5 |
| Age, mean $\pm$ SD, range; y | 40.0 $\pm$ 12.4, 14-74 | 35.4 $\pm$ 13.0, 18-60 |
| EDSS, median, range | 2.5, 0-5.5 | |
| MS type, %, RR/PP | 90.3/9.7 | |
| Patients with limited ambulation[a] | | |
| Number (%) | 53 (37.6) | |
| MWD in meters, median, range | 800, 100-4000 | |
| Patients with restricted ambulation[b] | | |
| Number (%) | 44 (31.2) | |
| MWD in meters, median, range | 600, 100-4000 | |

Abbreviations: MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; RR, relapsing–remitting; PP, primary progressive; MWD, maximum walking distance.
[a]Limited ambulation was defined as the inability to walk more than 4000 m.
[b]Restricted ambulation was defined as inability to walk more 2000 m.

All statistical tests were applied with a 2-tailed analysis and .05 as a level of significance.

## Results

A total of 141 MS patients with a mean age of 40.0 ± 12.4 years and an EDSS score ranging from 0 to 5.5 (median = 2.5) and 104 control healthy volunteers with a mean age of 35.4 ± 13.0 years participated in the study (Table 1). We observed that 53 out of the 141 (37.6%) MS patients had a "limited" ambulation defined by an MWD ≤ 4000 m. Forty-four subjects (31.2% of the whole population) had a so-called restricted ambulation, defined by an MWD ≤ 2000 m. The subgroup of MS patients who underwent a second analysis for the inter-rater ICC calculation and the whole MS patient population had comparable baseline characteristics (data not shown).

In the MS patient population, the time taken to perform the T100MW ranged from 30.6 to 197.9 seconds, with a median of 53.9 seconds, compared with a range of 33.1 to 62.1 seconds in healthy control volunteers with a median of 46.1 seconds (Table 2). The T25FW was performed in a time ranging from 2.9 to 20.7 seconds (median = 4.4 seconds) in MS patients and from 2.8 to 5.2 seconds (median = 3.7 seconds) in healthy control volunteers. Timed performances in both tests were significantly weaker for MS patients when compared with that of healthy control volunteers (both $P < .0001$). In every subpopulation of MS patients with EDSS scores ranging from 0 to 2.0, 2.5 to 3.5, and 4 to 5.5, both tests were also significantly altered when compared with healthy controls ($P = .018$, $P < .0001$, and $P < .0001$, respectively).

In healthy control volunteers (n = 104 patients), the test–retest ICC was slightly better for the T100MW (0.930) than for the T25FW (0.880). To compare the interrater reliability of both tests, a subgroup of 50 controls and 40 MS patients underwent a second testing by a different rater, and the interrater ICC was calculated. The interrater ICC of the T100MW and T25FW were not substantially different between controls (0.886 vs 0.884, respectively) and MS patients (0.953 vs 0.942, respectively).

The coefficient of variation (CV) was calculated to measure the dispersion of results obtained by both tests. Overall, the T100MW demonstrated less variability with a CV of 41% when compared with a CV of 45% for the T25FW. In patients with limited ambulation, the CVs for the T100MW and T25FW were 41% and 46%, respectively. The same was true for patients with restricted ambulation (T100MW CV = 40% vs T25FW CV = 46%). On examination of CVs by EDSS score, differences between the 2 walking tests were observed among patients with mid-range EDSS scores (2.5-3.5). The T100MW displayed less relative variability in this range of EDSS than the T25FW, with CVs ranging from 5% to 18% for the T100MW (Figure 1A) and from 14% to 25% for the T25FW (Figure 1B). It is important to emphasize that in this particular mid-range EDSS interval from 2.5 to 3.5, considered by definition to be fully ambulatory according to EDSS rules, 42.1% (16/38) of patients had a limited ambulation and 26.3% (10/38) had a restricted ambulation according to our aforementioned criteria.

Bland and Altman (BA) plots with limits of agreement were calculated to assess test–retest and interrater agreements. Between test and retest, the BA plots showed an equally good agreement for each of the walking tests (Figure 1C and D), with a similar number of patients beyond the limits of agreement. Between the raters, mean differences were also near 0 for both tests, with nearly all points falling within the limits of agreement (Figure 1E and F).

Spearman rank correlations (Table 3) showed that the T100MW and the T25FW correlated equally well with the EDSS, with $r$ values of .67 ($P < .0001$) and .67 ($P < .0001$), respectively. The overall correlation between the 2 tests was excellent ($r = .92$, $P < .0001$). In patients with "limited" or

**Table 2.** Time Values (Seconds) for the T100MW and the T25FW in Different Population Subsets

|  | T100MW, Median (Range) | T25FW, Median (Range) |
| --- | --- | --- |
| All MS patients, N = 141 | 53.9 (30.6-197.9) | 4.4 (2.9-20.7) |
| MS patients, EDSS 0-2.0, n = 63 | 49.3 (30.6-64.3) | 3.9 (2.9-5.4) |
| MS patients, EDSS 2.5-3.5, n = 38 | 56.5 (44.7-88.0) | 4.5 (3.3-7.7) |
| MS patients, EDSS 4.0-5.5, n = 40 | 78.0 (43.0-197.9) | 5.81 (4.0-20.7) |
| Healthy control volunteers, n = 104 | 46.1 (33.1-62.1) | 3.7 (2.8-5.2) |

Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 25-Foot Walk Test; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale.
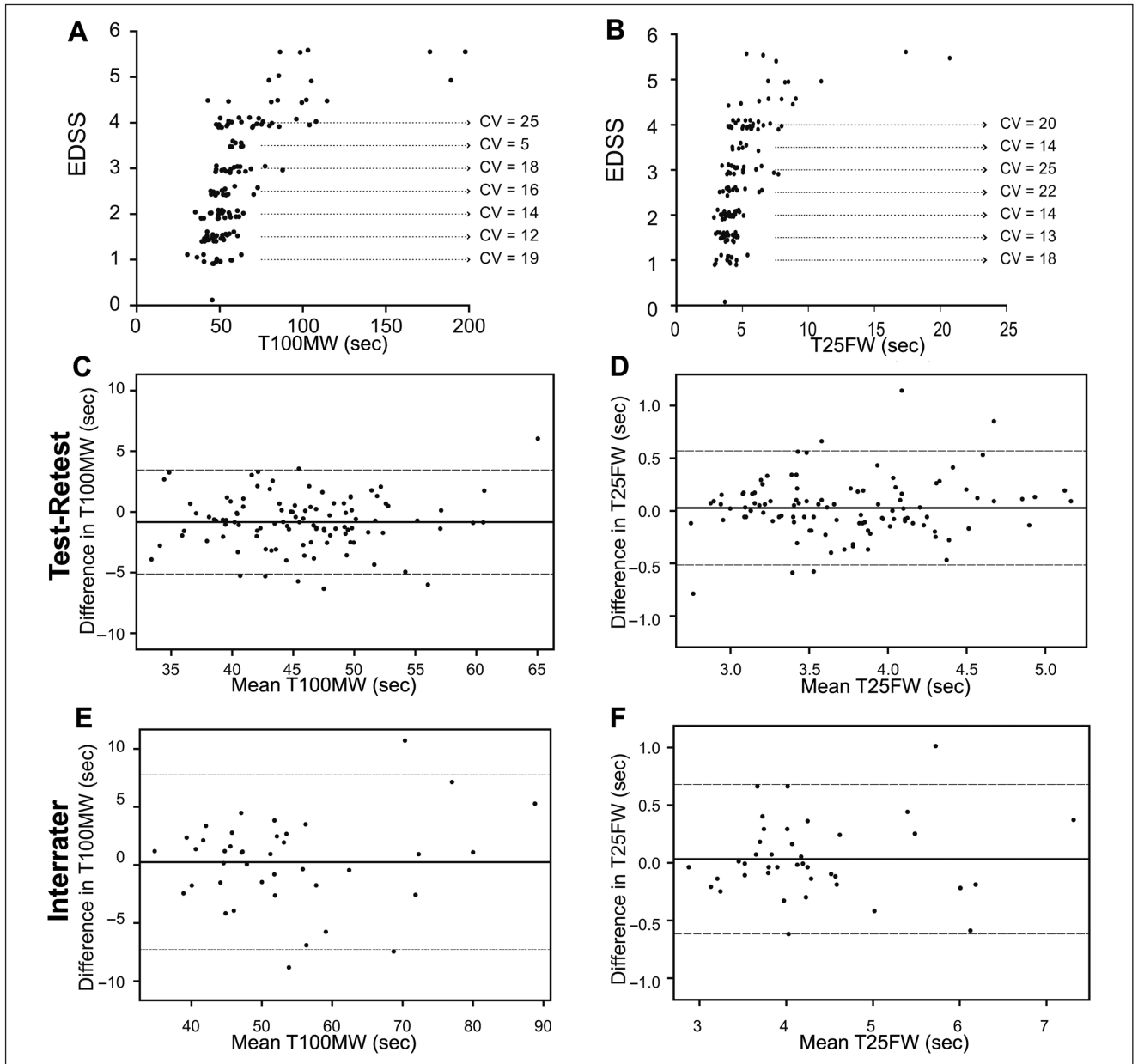


**Figure 1.** Coefficient of variation (CV, standard deviation divided by mean, expressed as a percentage) showing the distribution of the T100MW (A) and the T25FW (B) values by EDSS step, demonstrating less relative variability for the T100MW in the mid-range EDSS steps (2.5-3.5). Bland and Altman plots showing similar agreement across test and retest between the T100MW (C) and the T25FW (D). Equivalent agreements for the T100MW (E) and the T25FW (F) were also observed between raters. Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 100-Foot Walk Test; EDSS, Expanded Disability Status Scale.

**Table 3.** Spearman Rank Correlations Between Walking Tests, EDSS, and Walking Distance in Different MS Population Subsets

|  | Number of Patients | Spearman Rank Correlation[a] |
|---|---|---|
| Overall |  |  |
|   T25FW and EDSS | 141 | .6686 |
|   T100MW and EDSS | 141 | .6740 |
|   T25FW and T100MW | 141 | .9227 |
| Patients with limited ambulation[b] |  |  |
|   T25FW and walking distance | 53 | −.7121 |
|   T100MW and walking distance | 53 | −.7916 |
| Patients with restricted ambulation[c] |  |  |
|   T25FW and walking distance | 44 | −.6861 |
|   T100MW and walking distance | 44 | −.7738 |

Abbreviations: T25FW, Timed 25-Foot Walk Test; T100MW, Timed 100-Meter Walk Test; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale.
[a]All *P* values were <.0001.
[b]Limited ambulation was defined as the inability to walk more than 4000 m.
[c]Restricted ambulation was defined as the inability to walk more than 2000 m.
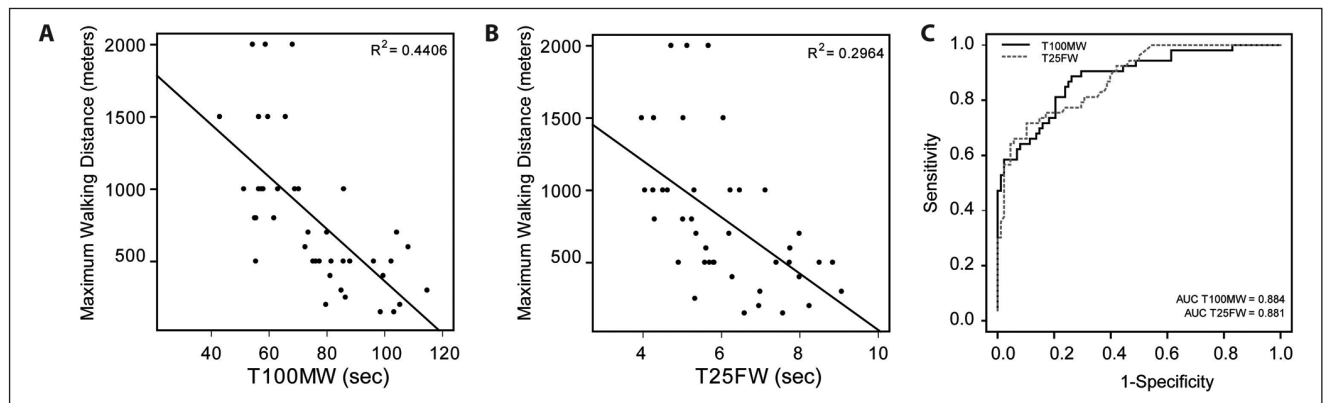


**Figure 2.** Correlation between the T100MW (A) and the T25FW (B) values and the maximum walking distance (MWD) and corresponding coefficient of determination ($R^2$). Receiver operator characteristic curve analysis of the T100MW (black line) and the T25FW (dashed grey line) and corresponding area under the curve (AUC) values (C). Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 100-Foot Walk Test.

"restricted" ambulation range for whom the MWD could be approximated, the T100MW correlated better with estimated MWD than the T25FW ($r = −0.79$ vs $r = −.71$ in the "limited" ambulation population and $r = −.77$ vs $r = −.69$ in the "restricted" ambulation population).

We also calculated the coefficient of determination ($R^2$) to estimate the proportion of variation in MWD explained by the walking tests in patients with "restricted" ambulation. The variation in MWD was explained for 44.1% with the T100MW (Figure 2A) versus 29.6% for the T25FW (Figure 2B). The area under the ROC curve (AUC) was estimated to compare the trade-off between sensitivity and specificity and the value of both tests in predicting limited ambulation (Figure 2C). We did not find a meaningful difference between the AUC of the T100MW (0.884) and the T25FW (0.881) in the overall population.

Finally, the MWS derived from the T100MW and the T25FW was significantly lower in MS patients ($1.8 ± 0.5$

and $1.7 ± 0.4$ m/s, mean ± SD, respectively) compared with healthy control volunteers ($2.2 ± 0.3$ and $2.1 ± 0.3$ m/s, mean ± SD, respectively); both $P < .0001$. The evaluation of ambulation impairment through the calculated MWS confirmed that performances were significantly altered for the 2 tests (T25FW and T100MW) in the global MS patient population compared with healthy control volunteers and in subsets of MS patients either with high (4.5-5.5) or low (≤3.5) levels of EDSS status (Figure 3A). Furthermore, we observed in individual performances that the T100MW MWS was very frequently faster than the T25FW MWS in healthy controls (data not shown) and in the MS population, as displayed by a positive absolute difference between both tests in a majority of MS patients (109/141 patients, 77.3% of the MS population, Figure 3B). In agreement with this finding, the mean T100MW MWS was found to be significantly higher than the T25FW MWS, both in healthy controls and in each subgroup of MS patients, defined by an EDSS ≤3.5 or ≥4.0 ($P < .0001$,
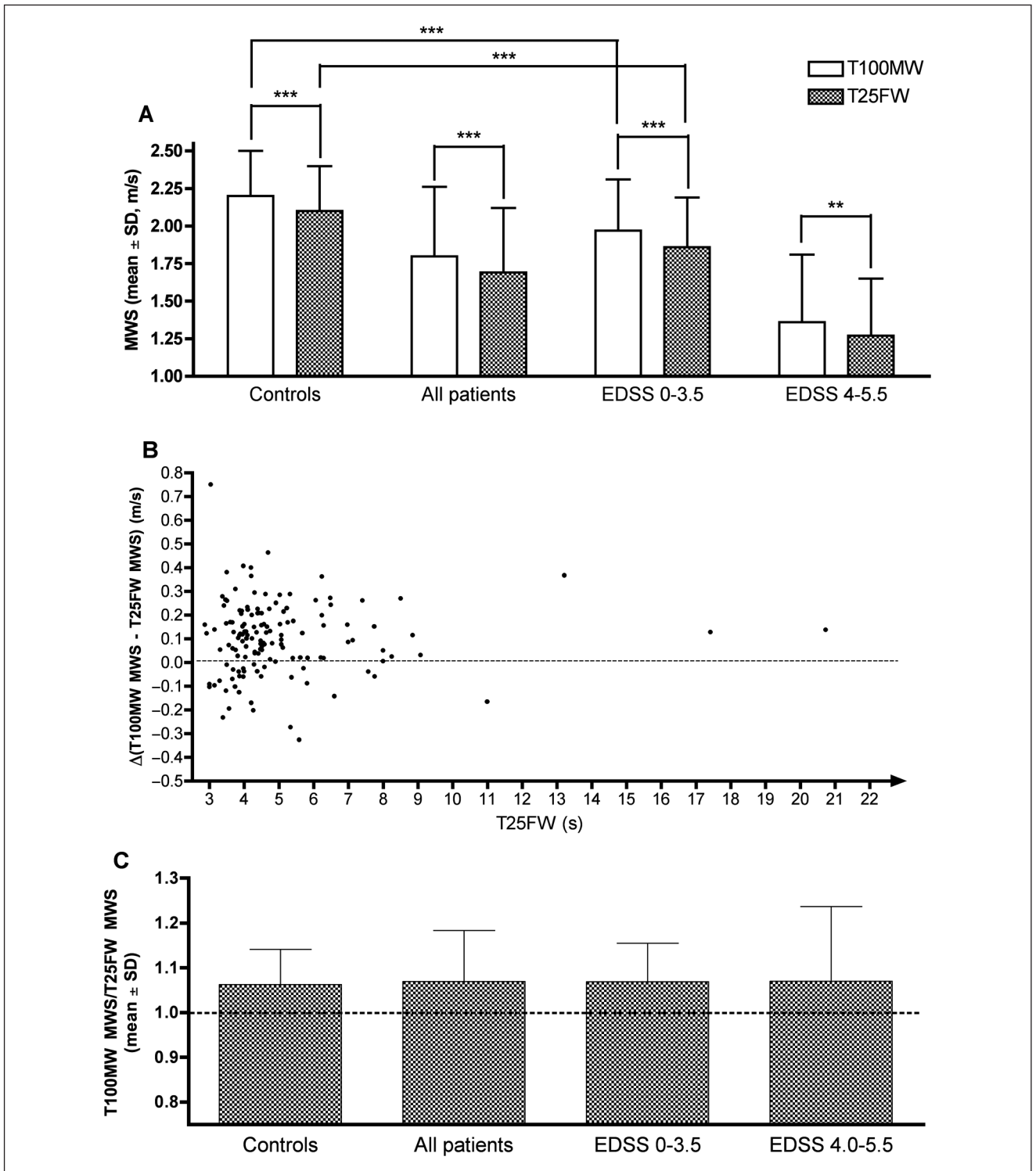
**Figure 3.** Mean walking speed (MWS) ± standard deviation assessed by the T100MW and the T25FW in healthy control volunteers, in all MS patients and in different subsets of EDSS range in the MS population (A); ***$P$ < .0001; **$P$ = .009; Note that all $P$ values were <.0001 for all respective comparisons of the 2 tests between MS patients and controls but only significant differences between controls and the low EDSS score group were highlighted. Absolute differences between the T100MW and the T25FW MWS in individual MS subjects were expressed as a function of T25FW performances (B). Mean ± standard deviation of T100MW MWS/T25FW MWS speed ratio values in healthy control volunteers, in all MS patients and in different subsets of EDSS scores (C). Abbreviations: T100MW, Timed 100-Meter Walk Test; T25FW, Timed 100-Foot Walk Test; EDSS, Expanded Disability Status Scale.

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$P < .0001$, and $P = .009$, respectively; Figure 3A). Consistently, in healthy controls as well as in different subsets of MS patients, the MWS over a 100-m distance was paradoxically ~7% higher than the MWS over 25 feet, as demonstrated by the mean values of the ratio between respective speeds calculated for each tests in individual subjects (Figure 3C).

## Discussion

The present study revealed minor differences favoring the T100MW over the T25FW, and a paradoxically higher MWS on the T100MW, both in control healthy subjects and in distinct subsets of our MS population.

The variability of the T25FW is related to different factors: practice effect, precision of the examining technician, motivational issues, and the level of accelerating capacity during the very first meters of the test. As a matter of fact, it can take half of the test for many patients to reach their maximum walking speed on a 25-foot-long distance, since the patient is asked to begin just behind the starting line. This is in line with the paradoxical finding of a higher MWS calculated on 100 m (T100MW) compared with the 25-foot distance (T25FW). One can assume that the fluctuant phase of acceleration in the first steps of the T25FW makes it a poor indicator of the real maximum walking speed over a short distance. Hence, variations in the T25FW duration are not solely representative of maximum walking speed differences.

The slightly better reliability and lower variability of T100MW indicate that other yet unidentified confounding factors may have less influence on a walking test based on a longer distance.

The T100MW appeared to be better correlated with the ambulation range (MWD) than the T25FW, in patients with "limited" (MWD $\leq$ 4000 m) or "restricted" (MWD $\leq$ 2000 m) ambulation. This was also suggested by the coefficient of determination calculation results. It is important to emphasize that the MWD was evaluated on a subjective basis between 500 and 4000 m, but patients' report of the MWD remains the most widely used approach in trial guidelines and has been shown to be reasonably correlated with values acquired from more sophisticated measures.[14]

When performing and comparing several types of gait evaluations, the order of assessment also has to be taken into account. In our study, one may argue that we did not assess the possible effect of the T25FW over the T100MW. However, the T25FW was always performed first. We postulated that the influence of a previous 7.62-m distance performed twice should only be of minor importance over the next 100 m walking speed performed after a 5 minute stop in between.

Beyond the attempts to develop new walking tests more predictive of the accurate MWD and maximum walking speed, there is a need for research efforts to gain more insight into the integrated comprehension of each individual tests with respect to the multiple identified parameters affecting the quality of ambulation, whether related to MS or not. Although diffuse cerebral white matter dysfunction may play a role in early walking disability, its main pathological substratum below an EDSS of 4.0 is likely to reflect mostly spinal cord demyelination and acute relapse–induced and/or chronic relapse–independent axonal loss or dysfunction, especially at the level of the pyramidal tracts.[15] In our study, the T25FW and the T100MW as well as the corresponding MWS displayed abnormal values in the low levels and mid-range EDSS values (EDSS $\leq$ 3.5), providing evidence of ambulation limitations at early stages of MS evolution. Such early walking limitations are not directly translated in the EDSS status calculation before the 4.0 milestones. The early insidious progression or relapse-driven accumulation of gait disability heavily contributes to the genesis of MS-related physical fatigue and its detection might be a guiding tool for assessing early specific therapeutic interventions. Moreover, in early stages of MS, any increase in the stringency of our analyses of walking performances may allow us to better delineate the spectrum of clinical improvement under highly active disease-modifying treatments.[16]

New walking tests, including a T25FW with a dynamic start (allowing a run-up of a few meters before the starting line), evaluations based on greater distances or longer time measurements,[17] speed ratios, and interval analysis may ultimately be even more informative in clinical trials and rehabilitation programs.[18] To evaluate walking fatigability and limitations of MWD, distance-based evaluations (such as 100-m or 500-m walking tests) may be more suitable than time-based evaluations (such as 2-, 3-, or 6-minute walking tests) for 2 reasons: (*a*) walking tests over a defined distance may allow patients to better dose their effort since they start with a concrete visuospatial representation of the length of the test and (*b*) in duration-based walking tests, the rater has to ask the patient to walk "as fast and as far as he/she can" over a defined time, which may be a confusing dual task in comparison to the more straightforward recommendation to walk "as fast as he/she can" in distance-based testing.

One may ultimately consider integrating multiple modalities of ambulation tests to develop composite walking indices that could be highly sensitive to change to better capture the efficacy of therapeutic interventions, especially in primary and secondary progressive forms of MS.

### Authors' Note

### Declaration of Conflicting Interests

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**7.2.2 Publication #2:** <u>Phan-Ba R</u>, Calay P, Grodent P, Delrue G, Lommers E, Delvaux V, Moonen G, Nagels G, Belachew S. A corrected version of the Timed-25 Foot Walk Test with a dynamic start to capture the maximum ambulation speed in multiple sclerosis patients. *NeuroRehabilitation.* 2012; 30(4): 261-6.

# A corrected version of the Timed-25 Foot Walk Test with a dynamic start to capture the maximum ambulation speed in multiple sclerosis patients

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**Abstract**. *Background*: No clinical test is currently available and validated to measure the maximum walking speed (WS) of multiple sclerosis (MS) patients. Since the Timed 25-Foot Walk Test (T25FW) is performed with a static start, it takes a significant proportion of the distance for MS patients to reach their maximum pace.
*Objectives*: In order to capture the maximum WS and to quantify the relative impact of the accelerating phase during the first meters, we compared the classical T25FW with a modified version (T25FW$^+$) allowing a dynamic start after a 3 meters run-up.
*Methods*: Sixty-four MS patients and 30 healthy subjects performed successively the T25FW and the T25FW$^+$.
*Results*: The T25FW$^+$ was performed faster than the T25FW for the vast majority of MS and healthy subjects. In the MS population, the mean relative gain of speed due to the dynamic start on T25FW$^+$ was independent from the EDSS and from the level of ambulation impairment. Compared to healthy subjects, the relative difference between dynamic versus static start was more important in the MS population even in patients devoid of apparent gait impairment according to the T25FW.
*Conclusion*: The T25FW$^+$ allows a more accurate measurement of the maximum WS of MS patients, which is a prerequisite to reliably evaluate deceleration over longer distance tests. Indirect arguments suggest that the time to reach the maximum WS may be partially influenced by the cognitive impairment status. The maximum WS and the capacity of MS patients to accelerate on a specific distance may be independently regulated and assessed separately in clinical trials and rehabilitation programs.

Keywords: Multiple sclerosis, gait, outcome measurement, maximum walking speed, acceleration, disability progression

## 1. Introduction

Ambulation impairment is one of the most prominent and frequent clinical feature of multiple sclerosis (MS) [1] with major consequences on patient's autonomy. Gait disturbances have a high impact on the personal, professional and social burden of this disease [2, 3]. The onset of permanent gait limitations is often conceived as a late process in the course of the disease, and ambulation is only taken into account beyond the score of 4.0 on the Expanded Disability Status Scale (EDSS) [4]. However, several studies have suggested that the restriction of ambulation performances might occur much earlier than previously considered [5–7]. Furthermore, the precise monitoring of walking capac-

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ities in MS patients is gaining more and more attention, since emerging rehabilitation techniques [8], symptomatic [9] and disease modifying [10] therapies are becoming increasingly effective with a substantial proportion of patients experiencing some degree of clinical improvement in specific conditions.

Although several alternative approaches have been developed [11–14], the Timed 25-Foot Walk Test [15, 16] (T25FW) is currently the most widely used test to evaluate locomotion in clinical trials. Although highly relevant to the characterization of patients' daily functional impairment, scarce data are available in regard of the precise gait-related physiological correlates of the T25FW. In fact, we recently demonstrated that the T25FW does not effectively measure the real maximum walking speed, since the mean walking speed (WS) is paradoxically higher on a longer distance (i.e. 100 meters) test [14].

Several hypotheses were proposed to explain this apparent discrepancy, such as a more important influence of the precision of the examining technician and of motivational issues in a short distance walk test. We also speculated that the relative duration and length of the accelerating phase during the very first meters of the test could contribute to the slower WS observed on a short distance walking test.

In order to investigate the potential weight of these first meters of acceleration in the T25FW performances, we proposed a corrected version of the test where a dynamic start is allowed 3 meters before the starting line (i.e. T25FW$^+$). We assumed that 3 meters, which represent nearly 40% of the full 25-foot distance was likely enough to reach a maximum walking pace for most MS patients. Hence, this paradigm allows to exclude or severely reduce the relative impact of the "acceleration phase" in the test and to compare the observed mean walking speed on the same distance with that of the conventional T25FW (i.e. with a static start right behind the line). To our knowledge no head-to-head comparison between static and dynamic starting protocols has ever been performed among the various methodologies previously used to assess the WS in MS [18,19].

## 2. Methods

Sixty-four patients with a diagnosis of relapsing-remitting or progressive MS according to the McDonald [20] criteria and 30 age and sex matched healthy controls used as a control group were enrolled in the study. We selected MS patients with a broad range of walking performances with an EDSS$\leqslant 6.5$.

The study protocol was approved by the local ethics committee from the medical faculty of Liège.

The T25FW was performed according to the published standardized instructions [15,16].

The T25FW$^+$ was also strictly following the guidelines of the T25FW [15,16], except that the subjects were allowed to take a 3 meters run-up before the starting line. This run-up was clearly demarcated on the ground. The raters were instructed for both tests to start the stopwatch as soon as the lead foot crossed the starting line of the 25-foot distance, and to stop it when the lead foot crossed the finish line.

The raters had been trained and certified for the administration of all the tests from the Multiple Sclerosis Functionnal Composite score (RP, PC or SB). EDSS scores were collected by certified EDSS-raters (RP or SB).

The T25FW and the T25FW$^+$ were performed as the first part of a multi-test evaluation during routine clinical evaluations, in an outpatient neurological MS department, between November 2009 and October 2010. The T25FW was first performed twice as well as the T25FW$^+$ after 5 minutes of break in between. For both tests, the results were expressed as the mean time of the 2 trials.

The Mean WS expressed in meters per second for both tests were obviously calculated by dividing 7.62m (i.e. 25 feet) by the time to perform the T25FW or the T25FW$^+$.

Non parametric unpaired t-test was used for between group comparisons, while non parametric paired t-test was used for within group comparisons. Pearson's correlation coefficient was used to assess the relationship between the two tests. All statistical tests were applied with a two-tailed analysis and 0.05 as a level of significance, and were performed using GraphPad Prism, version 4.0b for Macintosh, GraphPad Software, San Diego California USA (www.graphpad.com).

## 3. Results

The baseline characteristics of MS patients ($n = 64$) and healthy control volunteers ($n = 30$) are summarized in Table 1. No major differences were observed between the two populations. In the MS population, the median EDSS was 3.0 (ranging from 0 to 6.5). The distribution of the population throughout the different EDSS subgroups was harmonious.

Table 1
Characteristics of MS patients and control subjects

|  | MS patients | Healthy controls |
|---|---|---|
| Number of patients/controls | 64 | 30 |
| Gender (% female) | 59 | 71 |
| Age (median, range, years) | 39,15–64 | 25,18–60 |
| Body Mass Index (mean $\pm$ SD, kg/m$^2$) | 23,55 $\pm$ 4,2 | 25,18 $\pm$ 9,6 |
| EDSS (median, range) | 3.0, 0–6.5 | n.a. |
| EDSS 0–2.0 (number of patients, %) | 25 (39) | n.a. |
| EDSS 2.5–4.0 (number of patients, %) | 24 (37,5) | n.a. |
| EDSS 4.5–6.5 (number of patients, %) | 15 (23,4) | n.a. |
| MS type (CIS/RR/SP/PP, %)[1] | 9,4/65,6/12,5/12,5 | n.a. |
| Disease duration (mean $\pm$ SD, range, years) | 10,4 $\pm$ 9,3, 0–35 | n.a. |

1: CIS, Clinically Isolated Syndrome; RR, Relapsing-Remitting; SP, Secondary Progressive; PP, Primary Progressive.
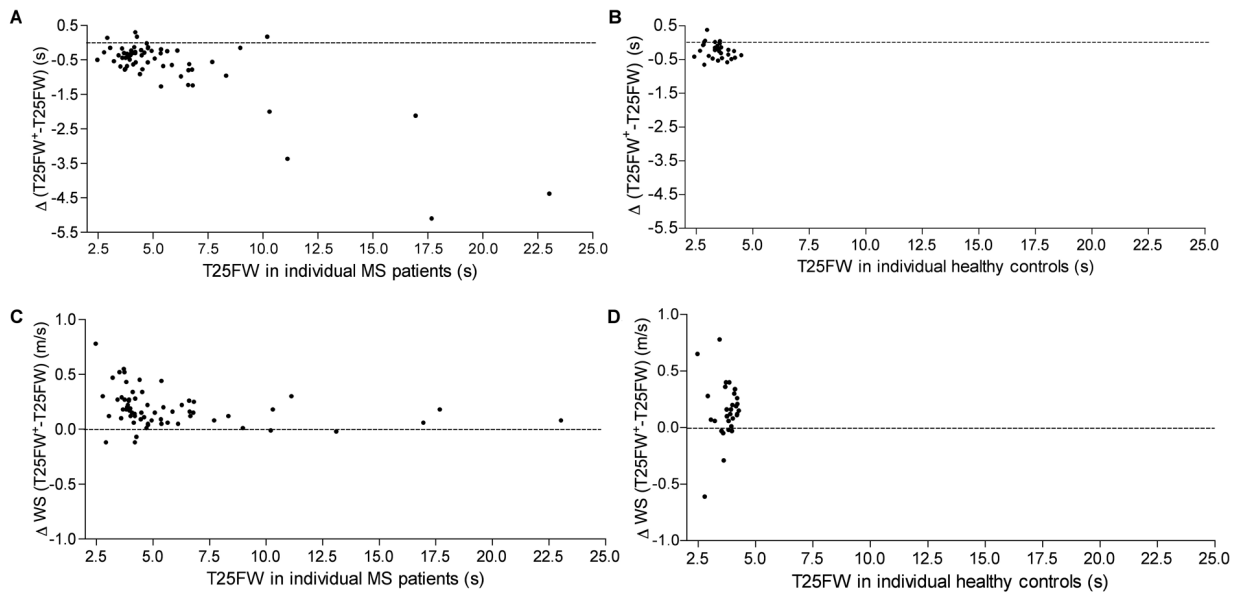


Fig. 1. Absolute difference between the T25FW$^+$ and the T25FW ($\Delta$T25FW$^+$-T25FW) in individual MS patients (A) and healthy controls (B). Absolute difference between the mean calculated walking speed (WS) in both tests ($\Delta$WS (T25FW$^+$-T25FW)) in MS patients (C) and healthy controls (D). All results were classified by increasing T25FW.

In both healthy control volunteers and MS patients, the two tests displayed a good correlation (Pearson's correlation coefficient = 0.8554 and 0.9791, both $p < 0.0001$, respectively).

As highlighted by individual absolute differences in time (Figs 1A and 1B) and in mean WS (Figs 1C and 1D), the vast majority of MS patients (92%, 59/64, Figs 1A and 1C) and healthy control volunteers (80%, 24/30, Figs 1B and 1D) performed consistently faster on the T25FW$^+$ than on the T25FW with varying levels of differences between the two tests (Fig. 1).

The difference between the two tests was further confirmed by a mean WS that was significantly higher for the T25FW$^+$ compared to the T25FW in MS patients (1.80 $\pm$ 0.65 vs 1.62 $\pm$ 0.57, respectively, mean $\pm$ SD,

m/s, $p < 0.0001$) and healthy controls (2.46 $\pm$ 0.43 vs 2.31 $\pm$ 0.37, respectively, mean $\pm$ SD, m/s, $p < 0.0001$) (Fig. 2A). Ambulation speed performances were also significantly slower for MS patients compared to that of healthy control volunteers in both tests ($p < 0.0001$ for both tests). The T25FW$^+$ was performed consistently faster than the T25FW in all subgroups of MS patients stratified according to their EDSS status (0 to 2.0, 2.5 to 4.0, and 4.5 to 6.5; all $p < 0.0001$, Fig. 2B). In order to dichotomize MS patients according to their normal versus abnormal walking performances, we fixed a threshold value of 4,43 seconds, corresponding to the mean T25FW of healthy controls plus twice the standard deviation. We then arbitrarily separated the MS population between the so-called "normal walker" group with
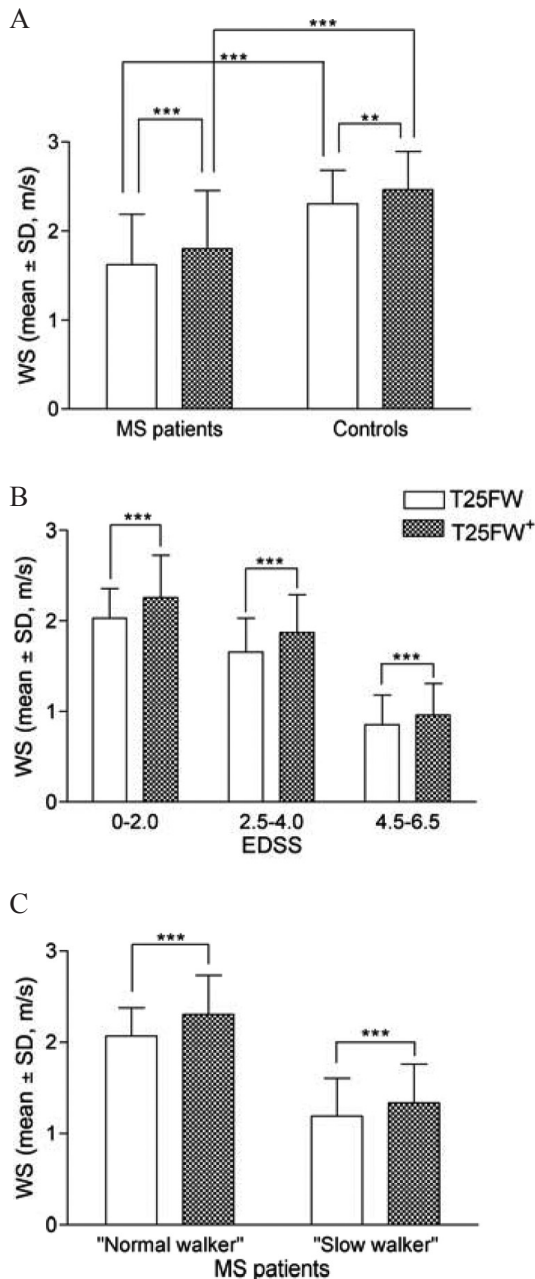
A



B



C



Fig. 2. Histograms depicting the mean walking speed (WS) on the T25FW$^+$ and T25FW in the global MS patient population and healthy controls (A), across different levels of disability status evaluated through the EDSS (B), and in "normal" versus "slow" walking MS patients (C).

a T25FW$\leqslant$ 4.43 s ($n = 31$, 48% of the population) and the "slow walker" group with a T25FW>4.43s ($n = 33$, 52% of the population). The mean WS was also significantly faster in the T25FW$^+$ both for the "normal" and "slow" walker MS groups ($p < 0.0001$, Fig. 2C).

We calculated the individual relative differences between WS in the two tests: i.e. the difference between WS on T25FW$^+$ minus WS on T25FW, divided by WS on T25FW$^+$. The mean relative difference between WS in the two tests ($\Delta$ WS (T25FW$^+$-T25FW)/WS T25FW$^+$) was significantly higher in MS patients compared to controls (10.2 $\pm$ 7.7%, versus 5.7 $\pm$ 9.1%, mean $\pm$ SD; $p = 0.0148$, Fig. 3A). No significant difference was found in the mean relative difference between WS in the two tests for the subgroups of MS patients at different levels of disability assessed by their EDSS status (Fig. 3A). The mean relative difference between WS in the two tests was also significantly higher in "normal" (10.0 $\pm$ 7.2%, mean $\pm$ SD, $p = 0.0461$) and "slow" (10.4 $\pm$ 8.2%, mean $\pm$ SD, $p = 0.0363$) walker MS patients compared with that of healthy control volunteers (5.7 $\pm$ 9.1%, mean $\pm$ SD) (Fig. 3B). No significant difference was found in this regard between "normal" and "slow" walker MS patients (Fig. 3B).

## 4. Discussion

The present study show that the time to reach the maximum WS has a significant impact in the results of the conventional T25FW, since a run-up of 3 meters can lead to a significantly higher mean WS measured on the same 25 foot distance, both in healthy control volunteers and in all subsets of MS patients. Removing part if not all of this accelerating phase to reach the maximum pace using a 3 meters run-up before the T25FW induced a more important difference between the two tests in MS patients compared to healthy volunteers, regardless of their EDSS status or their ambulation impairment.

The difference between the two tests was also significantly less pronounced in healthy volunteers than in "normal walker" MS subjects with no apparent ambulatory deficit. This observation may reflect the need for a longer distance of accelerating phase to reach the same maximum pace in MS patients, consequently performing a shorter proportion of the classical T25FW at their real maximum WS. This indicates that the maximum WS per se and the capacity of patients to accelerate on a specific distance are two distinct outcome measures, which can be differently affected by symptoms of MS. In comparison with the maximum WS, the acceleration capacity is likely to depend more on the motor reaction time to a simple command, which could be altered in case of mild cognitive dysfunction in MS patients.
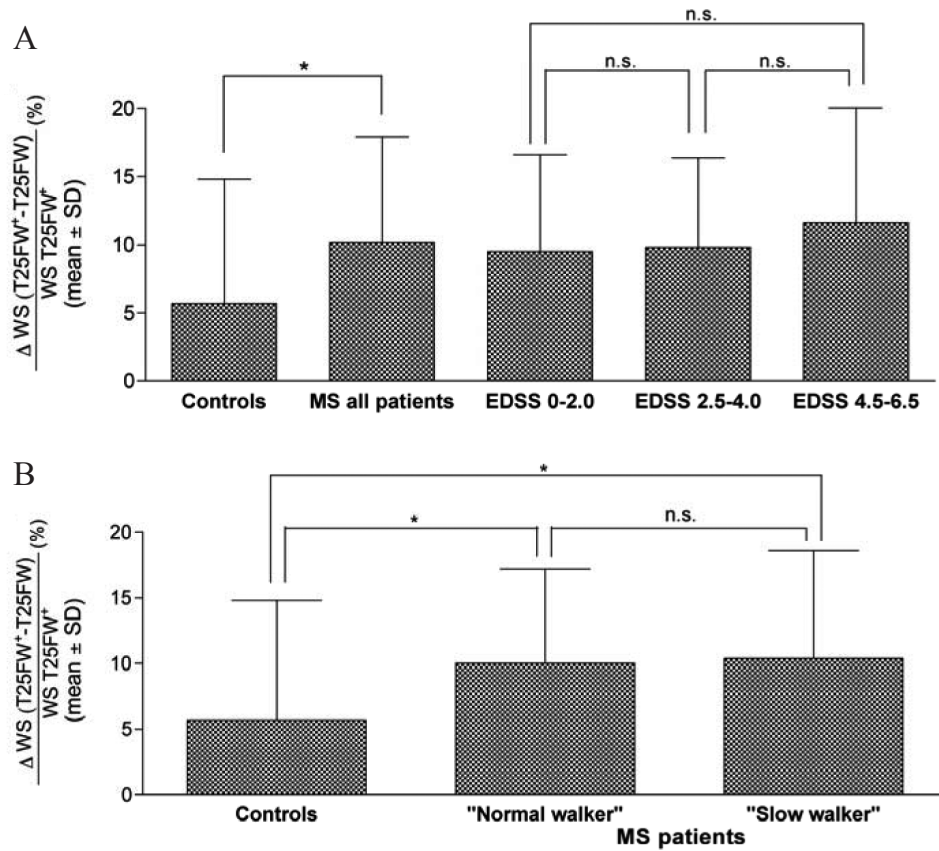
Fig. 3. Histograms depicting the mean relative difference between WS on the T25FW$^+$ and T25FW ($\Delta$WS (T25FW$^+$-T25FW)/ T25FW$^+$) in healthy controls, the global MS patients population (A), across different levels of disability status evaluated through the EDSS (A), and in "normal" versus "slow" walking MS patients (B).

Several studies have demonstrated that true walking impairment or even simple postural control abnormalities can be seen in the early course of MS [5–7,21] as well as in patients where the level of disability remained low or unapparent, with no clinically detectable signs of CNS lesions according to the Kurtzke functional system scores. Hence, beyond the typical pyramidal, proprioceptive, and cerebellar MS symptoms affecting ambulation, other factors that remains to be elucidated probably contribute to walking impairment in this disease. In this regard, the potential link between early cognitive impairment and gait disability should be further investigated [22]. In particular, the present data strengthen the hypothesis that the attention network and information processing speed systems, which are frequently altered early in MS [23,24] may contribute to gait and postural disturbances [5,22] at any stage of the disease course.

For clinical trials particularly when addressing progressive forms of MS, as well as for the field of neu-

rorehabilitation, these results emphasize that the classical T25FW needs to be revisited with a propelled start (T25FW$^+$) to better capture the real maximum WS of MS patients on short distances. Then only, should the T25FW$^+$ performances be compared to WS measurements performed using longer distance tests such as the Timed 100-Meters Walk Test [14]. This will allow the development of new insightful outcome measures through the calculation of ratios between WS measured on short and longer distances. We think such deceleration indexes may be reliable indicators of ambulation fatigue [25], which is present even at early stages of disease progression [26].

This refinement and improvement of ambulation outcome measures is a necessary step to increase their sensitivity and specificity in order to disentangle the effects of rehabilitation programs, disease-modifying and symptomatic treatments even at low levels of ambulation impairment, which is major component of patients' disability in multiple sclerosis.

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# Motor Fatigue Measurement by Distance-Induced Slow Down of Walking Speed in Multiple Sclerosis

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## Abstract

**Background and rationale:** Motor fatigue and ambulation impairment are prominent clinical features of people with multiple sclerosis (pMS). We hypothesized that a multimodal and comparative assessment of walking speed on short and long distance would allow a better delineation and quantification of gait fatigability in pMS. Our objectives were to compare 4 walking paradigms: the timed 25-foot walk (T25FW), a corrected version of the T25FW with dynamic start (T25FW+), the timed 100-meter walk (T100MW) and the timed 500-meter walk (T500MW).

**Methods:** Thirty controls and 81 pMS performed the 4 walking tests in a single study visit.

**Results:** The 4 walking tests were performed with a slower WS in pMS compared to controls even in subgroups with minimal disability. The finishing speed of the last 100-meter of the T500MW was the slowest measurable WS whereas the T25FW+ provided the fastest measurable WS. The ratio between such slowest and fastest WS (Deceleration Index, DI) was significantly lower only in pMS with EDSS 4.0–6.0, a pyramidal or cerebellar functional system score reaching 3 or a maximum reported walking distance ≤4000 m.

**Conclusion:** The motor fatigue which triggers gait deceleration over a sustained effort in pMS can be measured by the WS ratio between performances on a very short distance and the finishing pace on a longer more demanding task. The absolute walking speed is abnormal early in MS whatever the distance of effort when patients are unaware of ambulation impairment. In contrast, the DI-measured ambulation fatigability appears to take place later in the disease course.

## Introduction

Multiple sclerosis (MS) is a chronic multifocal disease of the CNS, which produces a wide range of neurological deficits. Ambulation impairment is recognized as a prominent feature of disability in MS, both by physicians and people with MS (pMS) [1]. The mechanisms underlying this locomotor impairment remain partially elusive. Besides functional system neurological deficits observed in the course of MS, it has been hypothesized that MS related motor fatigue can also impede gait performances [2]. In this context, motor fatigue is defined as the gradual decline of the maximal muscle strength during a constant mild to moderate physical exercise. Evaluation of ambulation limitation plays a central role in clinical scales [3] and composite outcome measures [4,5], which are used in the routine clinical practice and randomized clinical trials. The quantification of gait performances in MS remains usually limited to the simple anamnestic recall of the maximum reported walking distance (MrWD) [3], the stopwatch measurement of walking speed on short distance walking tests [4,5] through various settings and methodologies

[6–11], and the measurement of the maximum distance performed in a given time [12]. In contrast to maximum walking distance or maximum walking time, walking speed (WS) is believed to be a more stable parameter, which is less day-to-day variable and can be extracted from various walking paradigms [13,14]. Only few studies have investigated the behavior of pMS' performances on longer distance walking tests, with variable results and methodologies, as well as small population samples [2,12]. Gait is a complex motor behaviour that can only be roughly disentangled by a single walking test and we previously hypothesized that a multimodal walking assessment of gait in pMS would allow a better delineation and quantification of functional gait impairment in MS [7].

Since the onset of permanent gait limitations has often been conceived as a late process in the course of the disease, ambulation performances are only taken into account beyond the score of 4.0 in the Expanded Disability Status Scale (EDSS) [3]. However, several studies have suggested that the restriction of ambulation performances occurs much earlier than previously considered [15–

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17], but the precise timing and the extent of such limitations have been scarcely investigated.

In this work, we developed a 500-meter walking test to evaluate the mean WS of pMS in a demanding distance-based effort in comparison to the conventional short distance 25-foot test in a similar "as fast as possible" paradigm. Our objectives were (i) to determine the range of performances of pMS in this long-distance walking modality, (ii) to study the deceleration of the WS over this 500-meter distance in different subsets of pMS stratified according to their global EDSS, functional system (FS) scores according to Kurtzke and MrWD below or above the 4000 m milestone. These results emphasized that deceleration over the distance of a demanding ambulation test may be a valuable tool to assess locomotor fatigability in MS.

## Methods

### Ethics Statement

The "Comité d'Ethique hospitalo-facultaire" of the CHU of Liège approved the study procedure and written informed consent was received from all participants.

### Methods

A total of 81 subjects with a diagnosis of relapsing–remitting or progressive MS according to the McDonald criteria [18] and a MrWD≥500 m, and 30 weight- and sex-matched healthy volunteers used as a control group were enrolled in the study. pMS who had an EDSS from 4.5 to 6.0 were allowed to perform the walk tests using ambulatory assistive devices in case they would usually need it to walk the distance of 500 m or more. In such conditions (n = 9), the only requirement was that they were asked to use the same device for all tests. Ankle–foot orthosis was permitted if worn from onset for all evaluations. pMS who had experienced clinically disabling MS exacerbations with or without corticosteroid treatment within the last 3 months before study enrollment were excluded. Since it was previously shown that the time of the day does not interfere with ambulation outcome performances despite changes in subjective fatigue [14], pMS were tested at random periods of the day at their most convenient time.

pMS and healthy controls performed a multimodal walking assessment that comprised 4 tests, in the following order : the Timed 25-Foot Walk Test (T25FW, performed twice), a corrected version of the T25FW with a dynamic start (T25FW+, performed twice [10]), the Timed 100-Meter Walk Test (T100MW [7]), and the Timed 500-Meter Walk Test (T500MW). A period of rest of 15 minutes was allowed between each test to minimize interference due to potential test-related fatigue, and all demanding physical activities (such as rehabilitation sessions) were suspended in the last 24 hours prior to the assessment. Our subjects did not report any increased sense of subjective fatigue before starting a new test, especially before the last and most demanding T500MW. A slight worsening of the absolute results due to an increased motor fatigue in the T500MW cannot be excluded but this methodological bias was identical for all subjects.

All assessments were made by a certified MS nurse (PC) or by a physical therapist in charge of patients' rehabilitation programs (PG). EDSS scores were all collected by a certified EDSS rater (RP or SB).

The MrWD was evaluated as follows: control healthy volunteers all reported a MrWD superior to 4000 m, which was considered as "unlimited". pMS were asked whether they had the feeling that during the past 4 weeks their average walking performance had been unlimited and whether they thought they could walk for 4000 m or more without aid or rest. If they answered "yes", they

were considered to have an "unlimited" MrWD (i.e. ≥4000 m). pMS who considered themselves unable to walk 4000 m without aid or rest were asked to evaluate as accurately as possible their MrWD, which was defined as the maximum distance they thought they could walk without rest, and over which they would estimate they have a high risk of falling in case they would go on for a few meters more.

The T25FW was performed according to the published standardized instructions [4,5]. The T25FW+ was also strictly following the guidelines of the T25FW [4,5], except that the subjects were allowed to take a 3 meters run-up before the starting line [10]. This run-up was clearly demarcated on the ground. In order to minimize test-retest variability, the mean value of the two tests was used in the analysis of the T25FW and the T25FW+.

The T500MW was performed as 5 non-stop consecutive laps of the same path that served for the T100MW, as previously described [19], where interval times were recorded at each 100 m. The T100MW and T500MW were performed in a 3 m width corridor, devoid of obstacles. Running was prohibited. The subject was directed just behind the starting line and then instructed as follows: "I'd like you to walk this 100 (or 500) meter distance as quickly as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go." Timing started when the lead foot crossed the starting line. The examiner could not walk along with the patient as he/she completed the task. Timing was stopped when the lead foot crossed the finish line. The examiner then recorded the subject's walking time to within 0.1 second, rounding up or down as necessary. We rounded up to the next tenth if the hundredth of a second's place was ≥.05, rounded down if the hundredth of a second's place was <.05 (eg, 55.45″ would round up to 55.5″ but 55.44″ would round down to 55.4″).

The mean walking speed (MWS) expressed in meters per second were obviously calculated by dividing 7,62 m (i.e. 25 foot), 100 m or 500 m by the time to perform the respective distances.

Comparisons between groups were made with a student t-test and comparison within group with a paired t-test. All statistical tests were applied with a two-tailed analysis and 0.05 as a level of significance and were performed using GraphPad Prism, version 4.0b for Macintosh, GraphPad Software, San Diego California USA (www.graphpad.com).

## Results

The baseline characteristics of healthy control volunteers and pMS are detailed in Table 1. The distributions of gender and weight were comparable in both groups. The MS population was well balanced between different ranges of clinical disability stratified from EDSS 0 to 2.0, 2.5 to 3.5 and 4.0 to 6.0. Sixty percent of our MS population had an unlimited walking range defined by a MrWD≥4000 m, whereas approximately 40% reported to be able to walk between 500 m and 4000 m. MS patients were also stratified according to pyramidal, cerebellar and sensitive Kurtzke FS scores (all FS≤1, FS = 2 or FS = 3, no patients had an FS>3 in one of these three systems).

Mean timed performances in the 4 walking tests for healthy volunteers and for the different subgroups of pMS are presented in Table 2. For the T500MW, lap times per 100 m are also presented (Table 2). The mean walking speed (MWS) was compared between the 4 tests (Figure 1) in healthy volunteers and pMS according to their EDSS and MrWD. In healthy volunteers and in all subsets of pMS regardless of their EDSS or MrWD status, the order of calculated MWS values was T25FW+>T100MW> T25FW>T500MW. In all short and longer distance walking tests, the MWS was significantly lower for each subset of the pMS

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**Table 1.** Baseline characteristics of people with MS and healthy control volunteers.

| | pMS | Healthy controls |
|---|---|---|
| **Number** | 81 | 30 |
| **Age (years; mean ± SD)** | 40.16±11.35 | 30.3±10.4 |
| **Sex (female, %)** | 59 | 70 |
| **BMI[1] (mean ± SD)** | 23.72±4.13 | 23.33±3.37 |
| **MS type (CIS/RR/SP/PP[2], %)** | 10.1/61.7/14.6/13.4 | n.a. |
| **Disease duration (years; mean ± SD)** | 9.75±8.79 | n.a. |
| **EDSS[3] (median; range)** | 3.5 (0–6.0) | n.a. |
| **0–2.0 (n, %)** | 30, 37 | n.a. |
| **2.5–3.5 (n, %)** | 21, 25.9 | n.a. |
| **4.0–6.0 (n, %)** | 30, 37 | n.a. |
| **All FS[4]≤1 (n, %)** | 21, 25.9 | n.a. |
| **FS Pyramidal = 2, irrespective of other FS (n, %)** | 15, 18.5 | n.a. |
| **FS Cerebellar = 2, irrespective of other FS (n, %)** | 18, 22.2 | n.a. |
| **FS Sensitive = 2, irrespective of other FS (n, %)** | 34, 41.9 | n.a. |
| **FS Pyramidal = 3, irrespective of other FS (n, %)** | 25, 30.9 | n.a. |
| **FS Cerebellar = 3, irrespective of other FS (n, %)** | 31, 38.3 | n.a. |
| **FS Sensitive = 3, irrespective of other FS (n, %)** | 15, 18.5 | n.a. |
| **MrWD[5]** | | |
| **≥4000 meters (n, %)** | 49, 60.5 | n.a. |
| **≥500 meters; <4000 meters (n, %)** | 32, 39.5 | n.a. |

[1]: Body Mass Index (kg/cm$^2$);
[2]: clinically isolated syndrome/relapsing-remitting/secondary progressive/primary progressive - progressive-relapsing;
[3]: Expanded Disability Status Scale;
[4]: Kurtzke Functionnal System Score;
[5]: Maximum reported Walking Distance.
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population compared to healthy volunteers (statistics only shown graphically in Fig. 1A and 1B for pMS with EDSS≤2.0 or an apparently unlimited MrWD≥4000 m). MWS was also significantly lower for pMS at EDSS 4.0–6.0 compared to EDSS 2.5–3.5, in the 4 walking tests (Figure 1A, $p<0.001$ for all comparisons). No significant difference was found between the MWS of the pMS at EDSS 0–2.0 compared to EDSS 2.5–3.5 ($p = 0.1419$ for T25FW, $p = 0.1987$ for T25FW$^+$, $p = 0.1178$ for T100MW, and $p = 0.0783$ for T500MW). Finally, MWS was significantly higher for pMS with an MrWD≥4000 m compared to that of patients with an MrWD<4000 m in the 4 walking tests (Figure 1B, $p<0.001$ for all comparisons). When pMS were stratified according to pyramidal, cerebellar and sensitive Kurtzke FS scores, MWS data for all walking tests were very sensitive to detect significant differences between pMS with all FS≤1 and pMS with at least one FS = 2 or to detect significant differences between pMS with one FS = 2 and pMS with the same FS = 3 (Table S1).

In the T500MW, MWS was calculated over the five successive 100 m interval laps in order to capture the motor fatigue related deceleration occurring over time during this demanding motor task (Table 2, Figure 2). Different patterns of MWS evolution were observed in regard of the type of population studied (Figure 2). Regardless of the absolute differences of their MWS, healthy volunteers and pMS with a low level of disability (i.e. with an EDSS≤2.0, MrWD≥4000 m or all FS scores ≤1, Figure 2A, 2B and 2C, D, E, respectively) significantly decelerated during a 500 m walking task, as demonstrated by the comparison between the MWS of the first 100 m (T0–100MW) and the MWS of the

last 100 m (T400–500MW) during the test ($p = 0,0104$ for healthy volunteers, $p<0,0001$ for pMS with MrWD≥4000 m and $p = 0,0089$ for pMS will all FS scores ≤1). A mild acceleration at the end of the task (i.e. a higher MWS during the last 100 m - T400–500 - compared to the MWS over the T300–400) was observed in healthy volunteers and pMS with all FS scores ≤1, but only reached significance in the healthy volunteers population ($p = 0,0286$, data not shown). A highly significant deceleration was consistently observed in more disabled pMS with an EDSS 2.5–3.5 and 4.0–6.0 (Figure 2A), a MrWD between 500 and 4000 m (Figure 2B) or Kurtzke FS scores at 2 or 3 in the pyramidal, cerebellar or sensitive systems (Figure 2C, 2D and 2E, respectively). For these latter more disabled pMS groups all p values were <0,0001 for the comparisons of MWS between T0–100MW and T400–500MW.

In order to quantify ambulation fatigability over a demanding distance of effort, we proposed to integrate the fastest and the lowest measurable walking speeds over the different tested walking paradigms. The T25FW$^+$ MWS was previously confirmed to be a valid test to approach the fastest MWS of MS patients on a very short distance regardless of their acceleration capacity [10]. On the other hand, the mean finishing pace during the last 100 m of the T500MW (T400–500MW) appeared to be the lowest measurable speed over this fatigue inducing longer distance (Figure 2). The difference between T25FW$^+$ MWS and T400–500MW MWS was obviously significant in all pMS subgroups and healthy volunteers (Figure 3A, all $p<0,0001$). The individual performances of pMS showed that the relative deceleration observed between MWS values of the T25FW$^+$ and T400–

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**Table 2.** Timed performances[1] of respective populations in the different walking tests.

| | Controls (30) | pMS | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | All (81) | EDSS 0–2.0 (30) | EDSS 2.5–3.5 (21) | EDSS 4.0–6.0 (30) | MrWD≥4000 (49) | MrWD 500–4000 (32) |
| T25FW[2] | 3.38±0.53 | 4.91±2.10 | 3.88±0.64 | 4.21±0.76 | 6.44±2.73 | 4.04±0.77 | 6.25±2.72 |
| T25FW'[3] | 3.17±0.48 | 4.42±1.57 | 3.57±0.69 | 3.85±0.77 | 5.66±1.82 | 3.67±0.74 | 5.56±1.80 |
| T100MW[4] | 44.05±5.50 | 61.26±22.59 | 49.23±8.27 | 53.69±10.50 | 78.59±27.60 | 51.02±9.60 | 76.94±27.48 |
| T500MW[5] | 235.28±27.80 | 338.32±134.23 | 265.25±44.89 | 289.50±53.66 | 445.56±162.97 | 272.28±43.49 | 439.44±161.43 |
| 0–100 | 45.29±5.87 | 63.08±22.03 | 50.05±8.35 | 55.23±10.32 | 81.59±24.91 | 51.86±9.10 | 80.26±24.90 |
| 100–200 | 46.97±6.92 | 67.15±25.55 | 53.14±8.16 | 57.96±12.27 | 87.59±30.57 | 54.45±8.37 | 86.59±30.52 |
| 200–300 | 47.81±5.30 | 67.91±26.45 | 53.86±8.00 | 58.73±10.72 | 88.39±32.98 | 55.42±8.50 | 87.05±32.70 |
| 300–400 | 48.14±5.83 | 69.36±22.03 | 54.18±10.25 | 58.87±11.34 | 91.89±35.63 | 55.48±9.37 | 90.62±35.36 |
| 400–500 | 47.08±5.36 | 70.82±33.41 | 54.02±11.37 | 58.70±9.84 | 96.10±42.70 | 55.08±9.09 | 94.92±41.37 |
| | All FS≤1 (21) | FS P = 2 (15) | FS P = 3 (25) | FS C = 2 (18) | FS C = 3 (31) | FS S = 2 (34) | FS S = 3 (15) |
| T25FW[2] | 3.80±0.57 | 4.62±1.10 | 6.62±2.93 | 4.24±0.83 | 6.40±2.69 | 4.74±1.59 | 7.08±3.37 |
| T25FW'[3] | 3.48±0.67 | 4.20±0.91 | 5.78±1.94 | 3.89±0.73 | 5.66±1.80 | 4.30±1.20 | 6.12±2.26 |
| T100MW[4] | 48.04±7.39 | 58.20±13.16 | 80.80±29.24 | 52.96±9.01 | 78.86±27.10 | 60.29±18.37 | 83.43±34.25 |
| T500MW[5] | 254.86±29.69 | 320.97±76.14 | 456.92±173.69 | 291.83±60.60 | 446.01±158.83 | 336.86±115.79 | 467.63±196.46 |
| 0–100 | 48.48±7.43 | 61.81±16.02 | 83.03±25.99 | 55.27±10.71 | 81.75±24.14 | 62.85±19.98 | 85.54±28.51 |
| 100–200 | 51.37±4.96 | 65.48±16.90 | 88.72±32.74 | 57.68±11.63 | 88.13±29.79 | 67.03±23.19 | 92.11±35.75 |
| 200–300 | 52.07±5.85 | 64.63±14.48 | 90.64±35.27 | 58.98±11.35 | 88.41±32.22 | 67.11±21.49 | 94.18±40.53 |
| 300–400 | 51.62±5.93 | 64.33±14.94 | 94.76±38.06 | 59.98±13.44 | 91.90±34.79 | 68.54±23.09 | 96.59±44.14 |
| 400–500 | 51.33±7.11 | 64.71±15.34 | 99.77±45.38 | 59.92±14.34 | 95.82±41.79 | 71.33±31.39 | 99.21±48.64 |

The number of subjects in each subgroup is indicated in brackets next to subtitles.
1. each time performance is expressed in seconds, as mean ± SD;
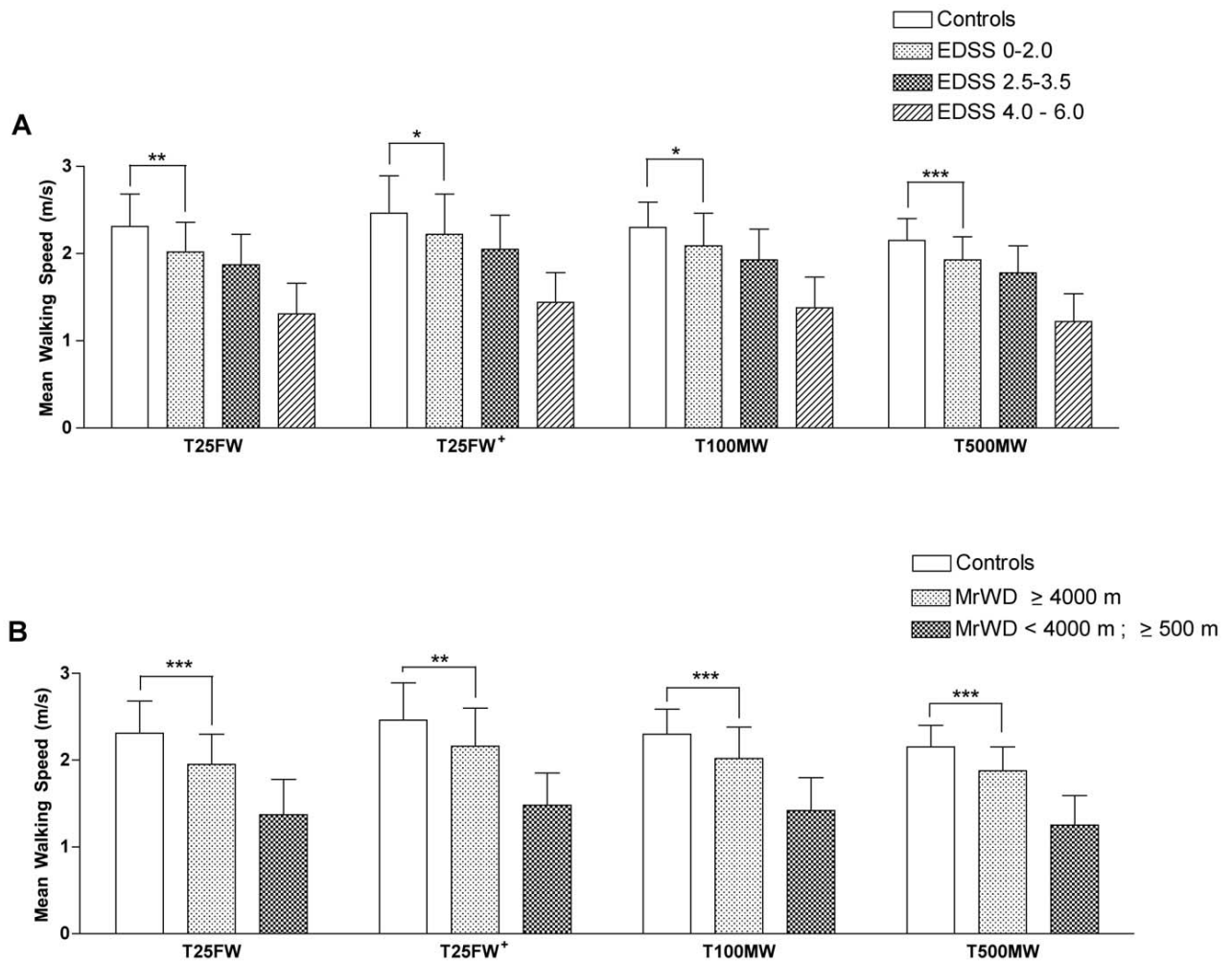2. Timed 25-Foot Walk Test;
3. Corrected version of the T25FW with a dynamic start;
4. Timed 100-Meter Walk Test;
5. Timed 500-Meter Walk Test with lap times evaluated for every 100 meter interval.
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**Figure 1. Mean walking speed (MWS) in healthy volunteers and in different subgroups of the pMS population.** The same general pattern of MWS differences across the different walking paradigms is observed in every group (T25FW+>T100MW>T25FW>T500MW). In the 4 walking tests, the MWS was significantly slower for each subset of the pMS population compared to healthy volunteers (all p<0,0001), including pMS with a low level of disability according to their EDSS status (EDSS≤2.0, A) or an apparently unlimited MrWD (MrWD≥4000 m, B).
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500MW (expressed as percentage of the T25FW+ MWS) was highly variable at all levels of walking impairment (stratified according to the T25FW, Figure 3B) and EDSS status (Figure 3C). We calculated the so-called Deceleration Index (DI) as the ratio between MWS of the T400–500MW divided by MWS of the T25FW+ (Figure 3D). Hence, the lower the DI ratio is, the more pronounced the patients were subjected to fatigue-related decrease of their walking pace over a long distance effort evaluated here by the 500 m dash. We observed a non significantly lower DI for pMS altogether compared to healthy controls (p = 0,088). pMS with an EDSS 4.0–6.0 had a significantly lower DI compared to pMS with an EDSS≤2.0 (p = 0.045). Compared to pMS with pyramidal, cerebellar and sensitive FS scores all ≤1, pMS with pyramidal or cerebellar FS at 2 had a non significantly lower DI (p = 0.33 and p = 0.42, respectively), whereas pMS with pyramidal or cerebellar FS at 3 had a significantly lower DI (p = 0.02 and p = 0.03, respectively). In contrast, pMS with a sensitive FS at 2 or 3 had a lower DI than pMS with all FS scores ≤1 but the differences were not significant for both comparisons. The DI of pMS subjects with a MrWD between 500 m and 4000 m was

significantly lower than for pMS with a MrWD≥4000 m (p = 0.0044). Finally, in contrast to the differences measured over absolute walking performances in short or long distance walking tests, no significant differences were observed for DI values between healthy volunteers and pMS with a low level of disability (i.e. with an EDSS≤2.0, MrWD≥4000 m or all FS scores ≤1, statistics not graphically shown on Figure 3D).

## Discussion

This study evaluated the relative walking speed performances of pMS compared to healthy volunteers on short and long distance walking tests. The groups were well matched according to BMI and sex ratio but the higher age in the pMS population compared to healthy volunteers may have slightly influenced the observed differences since the mean WS probably decreases with age [20].

All walking tests were performed in the "as fast as you can" configuration of the task in order to downsize motivational interferences, which are probably more prominent in a "preferred pace" modality [21].
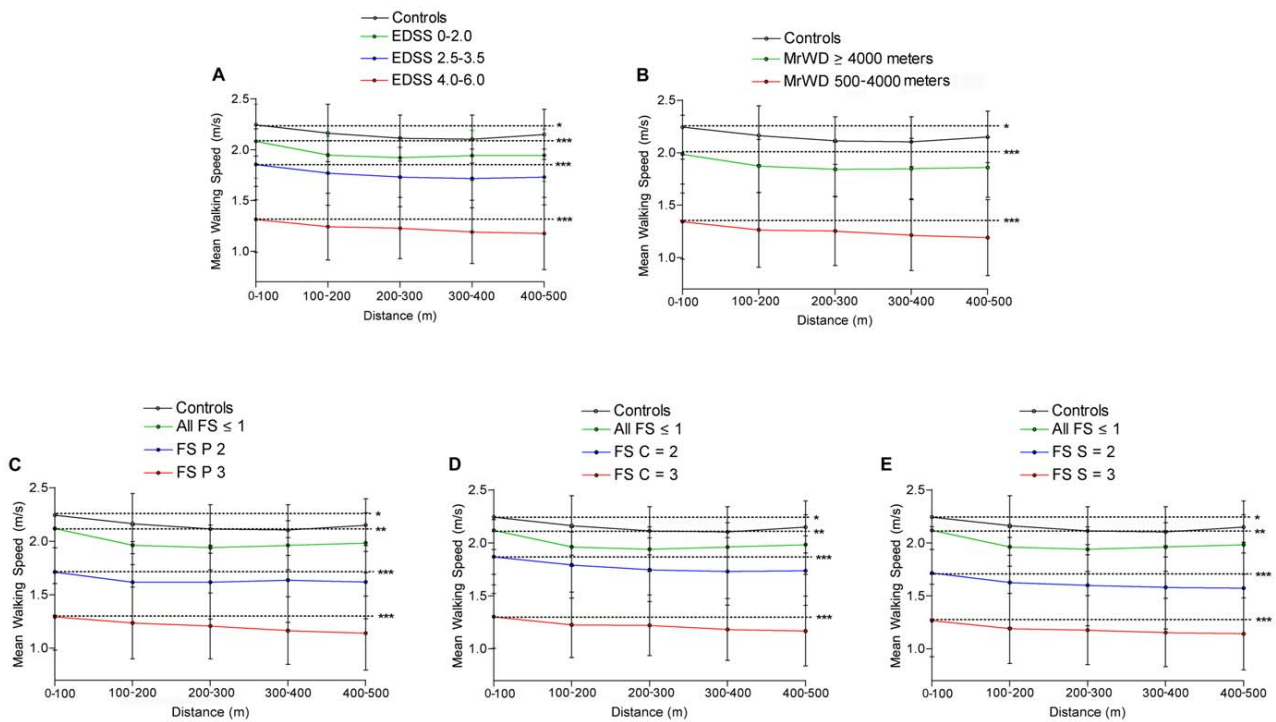
**Figure 2. MWS over five successive 100 m interval laps along the T500MW.** Subgroup analysis are presented in healthy volunteers and in different subgroups of the pMS population, stratified according to their EDSS (A), their maximum reported walking distance (MrWD) (B), and their pyramidal (C), cerebellar (D) and sensitive (E) functional scores (FS). The dashed lines represent the comparison between the "baseline" MWS of the first 100 m (T0–100MW) and the "final" MWS of the last 100 m (T400–500MW) for all subgroups. t-test values were *p<0.05, **p<0.01, ***p<0.0001.
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We demonstrated that in a cohort of pMS with mild to moderate disability and EDSS scores ranging up to 6.0, the evaluation of walking capacities over 500 m was an achievable goal, as long as assistive devices and short stops if needed were allowed for the more disabled patients between EDSS 4.5 and 6.0. The range of performances of our pMS population was globally in line with that of previous studies evaluating walking speed on similar distances [2,12,22].

The absolute performances of pMS obviously decreased according to the EDSS score, but a significant ambulation impairment was already seen on short and long distance in pMS with mild disability, with an EDSS status ≤2.0 or a MrWD≥4000 m [16,23].

We observed various patterns of deceleration in the different subsets of pMS over a 500 m walking task, regardless of absolute timed performances. As previously described, healthy volunteers and pMS with minimal disability (all FS scores ≤1, i.e. EDSS≤1.5) retained the ability to accelerate during the last 100 m of the 500 m task [2,12]. This final WS acceleration referred to the comparison between the T400–500 and the T300–400. However the mean WS of the T400–500 remained significantly lower than the mean WS of T0–100 for all subgroups. This observation is probably related to motivational issues ("end of the task" phenomenon), but it is striking that no final WS acceleration was observed in more disabled pMS, which may reflect the consequences of a more severe cognitive impairment or the translation of an increased spasticity or both aspects. For pMS with significant disability ranging from EDSS 2.0 to 6.0, the finishing pace of the last 100 m of the T500MW was the slowest measurable WS across the 4 walking tests. In contrast, the mean

WS on T25FW+ with a propelled start provided the fastest measurable WS in all pMS subgroups.

In order to assess locomotor fatigue, we identified the deceleration index (DI) as a ratio between the minimal (T400–500) and maximal (T25FW+) measurable WS. The origin of walking fatigability was not investigated in the current study, but it is noteworthy that pMS with a value of 3 on pyramidal or cerebellar FS scores demonstrated a significant alteration in the DI whereas pMS with a value of 3 on sensitive FS score did not. The individual DI of pMS were highly variable at all stages of walking impairment and the mean DI was significantly lower only in pMS with EDSS 4.0–6.0 or a maximum reported walking distance ≤4000 m. The mean DI remained similar to healthy volunteers in pMS with a low level of disability (i.e. with an EDSS≤2.0, MrWD≥4000 m) while absolute walking performances on short or long distance walking tests were all significantly abnormal in these pMS subgroups at early disease stages.

These results indicate that the DI measures the alteration of a sustained performance throughout a long demanding walking task, which is not captured by conventional absolute WS measurements, whether on a specific short or long distance, or in time-based settings. Such findings are consistent with the previous demonstration that motor fatigue is partially independent from motor (pyramidal) weakness [2,24].

In regard of the usual 500 m MrWD delineated by the EDSS calculation rules, this work suggested that a MrWD of 4000 m may be a more reliable threshold to better discriminate between "fully ambulatory" (as termed by John F. Kurtzke) and significantly limited pMS according to their walking performances.

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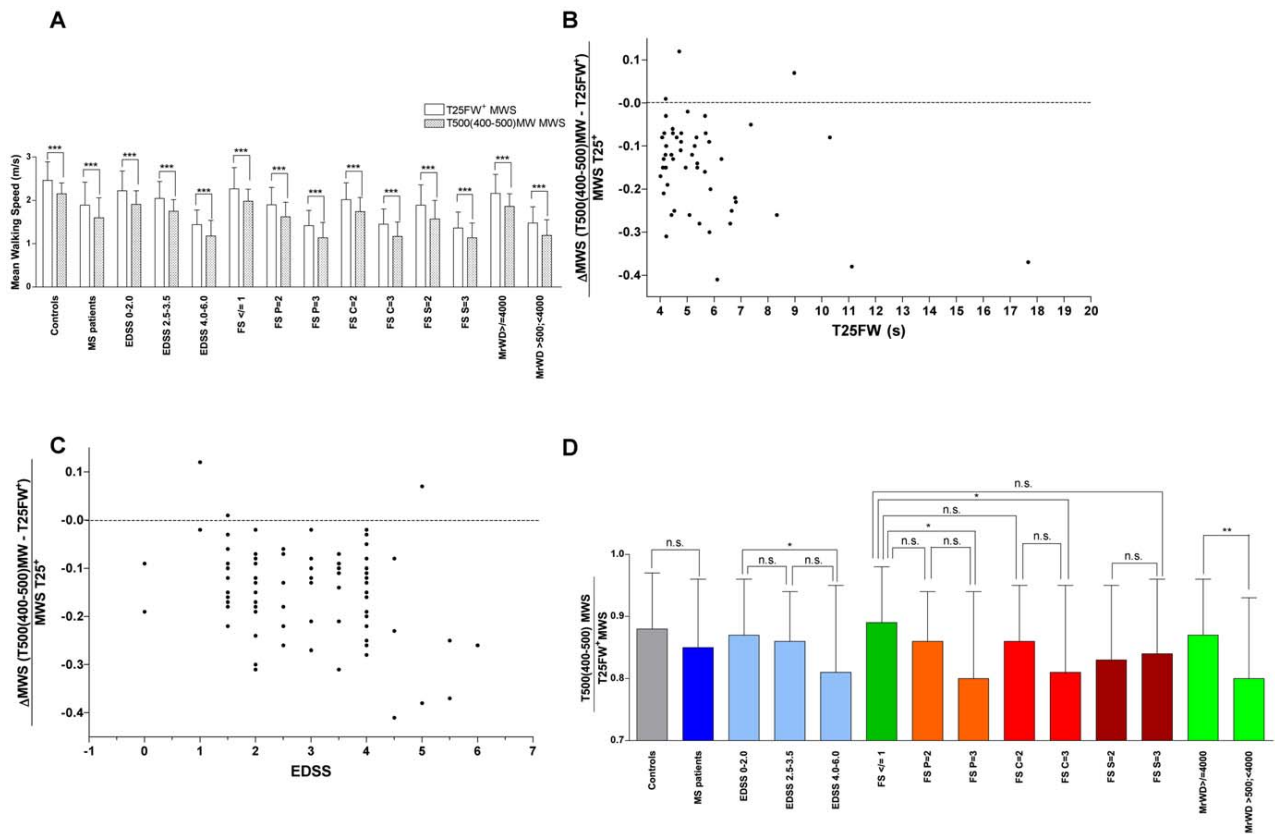
**Figure 3. Quantification of ambulation fatigability through the Deceleration Index (DI).** Ambulation fatigability was evaluated through the integration of the fastest (T25FW[+]) and the lowest (T400–500MW) measurable WS, which were obviously highly statistically different in all pMS subgroups and healthy volunteers (A, all p<0,0001). Absolute WS differences were however very similar between all groups (ranging from 0.22 m/s for FS S = 3 to 0.31 m/s for EDSS 2.5–3.5 and Controls). This is why further comparisons between groups were focused on relative WS changes. No significant correlation could be found between the individual values of relative deceleration evaluated by the difference of MWS on the T25FW[+] and on the T400–500MW (expressed as percentage of the T25FW[+] MWS) and the level of walking impairment according to the T25FW (B) or the EDSS status (C). Deceleration Index (DI) calculated as the ratio between MWS of the T400–500MW divided by MWS of the T25FW[+] (D) in healthy volunteers and in different subgroups of the MS population.
doi:10.1371/journal.pone.0034744.g003

Although the 4000 m was chosen arbitrarily, a higher threshold may have led to consider healthy untrained individuals as disabled.

It was outside the scope of the present cross-sectional analysis to investigate the sensitivity to change of the walking tests and their relevance in self-reported quality of life of pMS but it will be prospectively addressed in a future study.

In conclusion, we provided evidence that sequential gait evaluation over a 500 m distance is a valuable tool to measure the decrease of WS over the duration of a demanding walking task. The combination of short and long distance "as fast as possible" walking tests to assess a relative deceleration (DI) is a coherent paradigm to allow a reliable measurement of locomotor fatigue. Our data suggest that ambulation fatigability is at least partially independent from absolute performances on a given distance, which are abnormal early in MS, while the DI is altered later in the disease course. The DI may be a sensitive tool to detect and measure walking fatigability even though it is less sensitive than absolute mean WS on short and long distances to detect early walking impairment. Further work will be needed to clarify the clinical relevance of such a new performance-based measurement.

## Supporting Information

**Table S1** Statistical comparisons of the MWS (Student T-tests) in the T25FW, the T25FW[+], the T100MW and the T500MW across different subsets of the pMS population stratified according to their pyramidal (P), cerebellar (C) and sensitive (S) Functional System Scores (FS).
(DOC)

## Author Contributions

Conceived and designed the experiments: RP SB. Performed the experiments: RP GD EL VD PG PC SB. Analyzed the data: RP GM SB. Contributed reagents/materials/analysis tools: PG PC. Wrote the paper: RP SB.

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**A new low-cost and non-intrusive feet tracker. *Workshop on Circuits,***
***Systems and Signal Processing (ProRISC).* 2011:382-7.**

# A new low-cost and non-intrusive feet tracker

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*Abstract*—Capturing gait is useful for many applications, including video-surveillance and medical purposes. The most common sensors used to capture gait suffer from significant drawbacks. We have therefore designed a new low-cost and non-intrusive system to capture gait. Our system is able to track the feet on the horizontal plane in both the stance and the swing phases by combining measures of several range laser scanners. The number of sensors can be adjusted according to the target application specifications. The first issue addressed in this work is the calibration: we have to know the precise location of the sensors in a plane, and their orientations. The second issue addressed is how to calculate feet coordinates from the distance profiles given by the sensors. Our method has proven to be robust and precise to measure gait abnormalities in various medical conditions, especially neurological diseases (with a focus on multiple sclerosis).

*Index Terms*—gait analysis, gait recognition, multiple sclerosis, range laser scanners

## I. Introduction

Capturing gait is useful for many applications, such as person [1], gender [2], or age [3] identification. Gait analysis is also useful for medical purposes, since ambulation impairment is a frequent symptom of a broad range of diseases, including multiple sclerosis where quantitative evaluation of gait performances is a good indicator of disease activity.

The most common sensors used to capture gait are cameras (*cf* [4], [5], [6]), electronic walkways (such as the GAITRite [7]), and motion capture systems (*e.g.* Coda Motion units CX1 [8]). All these systems present significative drawbacks such as unreliability of the information obtained with color cameras since it depends on lighting conditions. The GAITRite system is expensive and provides only information regarding the position of the feet in the stance phase. Motion capture (mocap) systems are also expensive and require that the users wear (active or passive) tags, which is not possible in most applications.

We have designed a new system to capture gait. As feet paths are highly informative for gait recognition [9] and most of medical gait-based purposes, our aim is to determine the position of the feet in real time. Each foot is considered as a point in an horizontal plane, and the vertical movements are ignored. Many useful informations may be easily extracted: walking speed, distance between feet over time, swing phase duration, gait asymmetry, etc.

We use several range laser scanners to analyze an horizontal slice of the scene. Our platform is cheaper than existing motion capture systems and GAITRites, is insensitive to lighting
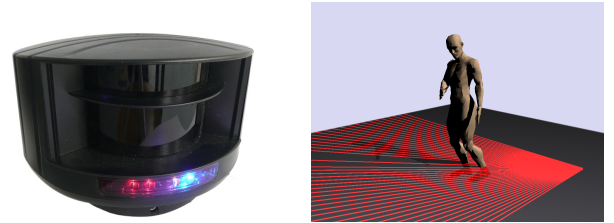


Figure 1. Our feet tracker is based on the distance profiles provided by a set of range laser scanners (*e.g. BEA LZR-i100*) placed in a horizontal plane.

conditions, and does not require the persons to wear any tag. Moreover, it captures the feet positions in both the swing and the stance phases.

The outline of this paper is as follows. Section II describes the selected sensors, their advantages, and their limitations. In Section III, we detail how our system is calibrated: the precise location of the sensors in a plane and their orientations are to be determined. Section IV is devoted to the tracker itself: it describes the way feet (*i.e.* ankle section plane) coordinates are calculated from the depth profiles given by the sensors. Section V focuses on the use of our tracker in a real medical application. Finally, we give a short conclusion in Section VI.

## II. Sensors

We use several range laser scanners to analyze an horizontal slice of the scene. The number of sensors can be adjusted according to the target application specifications. Using several sensors allows us to reduce occlusions, or to cover a wider area. The scanned plane is chosen to be located at $15\,cm$ above the floor, which is right above the tibio-tarsal joint of the ankle in a barefoot configuration for adult individuals in stance phase, and remains above the maximal height reached by the feet during the swing phase, allowing the range laser scanners to track the feet even in the swing phase.

### A. Selecting the sensors

In previous works [10], [11], we used the range laser scanners *BEA LZR-p200*. Those sensors have been designed to monitor a door of $4\,m$ wide and $4\,m$ high, and therefore their behavior is undefined when the distances to measure exceed $4\sqrt{2} = 5.65\,m$. For some applications, it is mandatory to reach larger distances. For example, the $25\,ft$ distance ($7.62\,m$) is a common requirement for standardized tests concerning multiple sclerosis. That is why, in this work, we

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have chosen another model of the same family: the *BEA LZR-i100* (see Figure 1). These have only a limit distance of $10\sqrt{2} \simeq 14.14\,m$, which is large enough for most applications.

The selected sensors are adequate for measuring distances with a high precision, without any reflector. They are small, and easy to place in various environments. Note that the risk of interference between sensors is negligible, and therefore it is safe to use several sensors to scan the same plane.

The sensors measure distances in 274 directions spanning $96°$, in a plane, at $15\,Hz$. Their resolution is $1\,mm$. In practice, we observe a temporal variation of a few millimeters, and seldom a few centimeters, on the acquired distances. It should be noted that the sensors are strongly disturbed by highly reflective materials such as metal, and black materials (in the infrared band). It should also be noted that at discontinuities, the sensors provide a random measure between the minimum and the maximum distance. Therefore, the sensors may see points where there is no object in the scene (these points are named *outliers* in the following). Robustness to outliers is therefore mandatory.

### B. Behavior in dynamical scenes

The field of view of $96°$ is obtained thanks to an internal rotating mirror. As the mirror has to turn $48°$ to cover the $96°$, a frame is acquired in $\frac{1}{15} \cdot \frac{48}{360}\,s \simeq 9\,ms$.

An object of $10\,cm$ (*i.e.* the typical size of a leg) located at $1\,m$ from the sensor is viewed inside of a $5.7°$ large angle, and therefore in $\frac{5.7}{2} \frac{1}{15} \frac{1}{360}\,s \simeq 0.52778\,ms$. For a walking speed of $5\,km/h$, the maximal speed of the feet is approximately $16\,km/h$. In consequence, a foot can move by $\frac{0.52778}{1000} \frac{1600000}{3600} \simeq 0.235\,cm$ during the data acquisition. As this displacement is negligible, the selected sensors are quick enough to track feet with high precision.

However, it should be stressed that there exist no ways to synchronize the sensors. With multiple sensors, merging the information provided by the sensors is required. Unfortunately, there may be a temporal gap of $\frac{1}{15}\,s$ between the data to be fused. For a walking speed of $5\,km/h$, this is equivalent to an uncertainty of $29.6\,cm$ on a foot position in the worst case. Clearly, this source of uncertainty is dominant. Note however that this uncertainty is only along the path followed by the foot.

### C. Towards a simple model of the sensors

In this paper, we assume that the sensors are punctual. This implies that the 274 lines-of-sight are concurrent and that the intersection point is located in the sensor. Under these assumptions, the distance measured between the sensor and a visible point of the scene is the distance between the point and the aforementioned intersection. It follows that, to obtain the coordinates of the 274 points seen by a sensor, a simple polar to cartesian transform suffices.

### III. The calibration procedure

The goal of the calibration procedure is to determine the precise location of the sensors in the room, and their orientations. This knowledge is mandatory to fuse the information

provided by different sensors. Of course, this procedure has to be done only once, after the installation of the sensors in the room. In this section, we present a semi-automatic calibration procedure.

It should be stressed that the calibration has to be very accurate. An error of $0.075°$ on the orientation of a sensor has for consequence an error of $1\,cm$ on the location of a point seen at $7.62\,m$. A well designed calibration procedure is therefore needed.

### A. Description of our calibration procedure

In the proposed procedure, a cylinder is successively placed in the room at a few places. Each sensor has its own local cartesian coordinate system. Each time the cylinder is displaced, its center coordinates are estimated in the local coordinate system of each sensor.

The passage from one local coordinate system to another is done by a transformation composed of translation and rotation. The calibration is equivalent to determining these transformations. The cylinder has to be placed a least at two different locations, but repeating the operation a dozen of times, to take advantage of the least squares error reduction mechanism, helps to improve the calibration. Note that there is no need to increase the number of locations if the number of sensors increases. Also, we assume that the cylinder is visible to all sensors.

Let $\left(C_{xi}^s, C_{yi}^s\right)$ be the coordinates of the cylinder in its $i$-th position expressed in the local cartesian coordinate system of sensor $s$. If, in the local cartesian coordinate system of sensor 0, the sensor $s$ is located at $\left(\Delta_x^s, \Delta_y^s\right)$ and is looking in the direction $\theta^s$, we have $\forall i$

$$\begin{pmatrix} \cos\left(\theta^s\right) & -\sin\left(\theta^s\right) & \Delta_x^s \\ \sin\left(\theta^s\right) & \cos\left(\theta^s\right) & \Delta_y^s \end{pmatrix} \begin{pmatrix} C_{xi}^s \\ C_{yi}^s \\ 1 \end{pmatrix} = \begin{pmatrix} C_{xi}^0 \\ C_{yi}^0 \end{pmatrix} \quad (1)$$

Therefore, the position and the orientation of the sensor $s$ can be found solving the following linear equation:

$$\begin{pmatrix} C_{x0}^s & -C_{y0}^s & 1 & 0 \\ \vdots & \vdots & \vdots & \vdots \\ C_{xp}^s & -C_{yp}^s & 1 & 0 \\ C_{y0}^s & C_{x0}^s & 0 & 1 \\ \vdots & \vdots & \vdots & \vdots \\ C_{yp}^s & C_{xp}^s & 0 & 1 \end{pmatrix} \underbrace{\begin{pmatrix} \cos\left(\theta^s\right) \\ \sin\left(\theta^s\right) \\ \Delta_x^s \\ \Delta_y^s \end{pmatrix}}_{\text{unknowns}} = \begin{pmatrix} C_{x0}^0 \\ \vdots \\ C_{xp}^0 \\ C_{y0}^0 \\ \vdots \\ C_{yp}^0 \end{pmatrix} \quad (2)$$

As this system is overconstrained when the cylinder is placed more than two times, the solution has to be determined in the least-squares sense.

In practice, we manage to ensure that the cylinder is the only moving object in the scene during calibration. We apply a background subtraction to the signal provided by each sensor, in order to filter out the static elements of the scene and to keep only the points corresponding to the cylinder. To decrease the sensitivity to outliers, our implementation uses the RANSAC algorithm to obtain robust circle fits.

The remainder of this section is devoted to the comparison of four circle fitting procedures (three well known and a new one), and to the selection of the best one. In our case, the data points are sampled along a small arc of circle.

## B. Circle fitting methods

Let $(x_1, y_1)$, $(x_2, y_2)$, ... $(x_n, y_n)$ be the points by which we want to get a circle of radius $R$ and center $(C_x, C_y)$ to pass trough. The key to a solution consists in finding an optimization criterion that leads to equations easy to solve. For example, the least squares criterion

$$\min \sum_{i=1}^{n} \left( \sqrt{(x_i - C_x)^2 + (y_i - C_y)^2} - R \right)^2 \qquad (3)$$

is difficult to handle since it leads to a nonlinear problem that has no closed form solution (with iterative methods, one is faced with questions related to convergence, plateaus, valleys, and to the initial guess). Surprisingly, fitting a circle to a cloud of points is a difficult problem. A entire book devoted to the subject has been published recently [12].

*1) Kåsa's method:* Instead of the criterion (3), Kåsa proposed in [13] to use the criterion

$$\min \sum_{i=1}^{n} \left( (x_i - C_x)^2 + (y_i - C_y)^2 - R^2 \right)^2 \qquad (4)$$

Both criterions (3) and (4) are equivalent if there exists a circle passing through all points. However, the solution may be different if the observations are noisy. If $R$ is an unknown, Kåsa's criterion is easier to deal with, because it leads to a unique and explicit solution. We denote the centered moments:

$$\mu_{ab} = \frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x})^a (y_i - \bar{y})^b \qquad (5)$$

where $\bar{x} = \frac{1}{n} \sum_{i=1}^{n} x_i$ and $\bar{y} = \frac{1}{n} \sum_{i=1}^{n} y_i$ are the coordinates of the gravity center of the cloud of points. With Kåsa's criterion, the optimal center of the circle is given by

$$C_x = \bar{x} + \frac{1}{2} \frac{\mu_{02}(\mu_{30} + \mu_{12}) - \mu_{11}(\mu_{03} + \mu_{21})}{\mu_{20}\mu_{02} - \mu_{11}^2} \qquad (6)$$

$$C_y = \bar{y} + \frac{1}{2} \frac{\mu_{20}(\mu_{03} + \mu_{21}) - \mu_{11}(\mu_{30} + \mu_{12})}{\mu_{20}\mu_{02} - \mu_{11}^2} \qquad (7)$$

*2) Our method: Kåsa's criterion with $R$ known:* If the radius is known, then the optimal center corresponding to Kåsa's criterion may differ because we cannot write anymore

$$\frac{\partial}{\partial R} \sum_{i=1}^{n} \left( (x_i - C_x)^2 + (y_i - C_y)^2 - R^2 \right)^2 = 0 \qquad (8)$$

Without loss of generality, let's assume that $\bar{x} = 0$ and $\bar{y} = 0$. This can be obtain by translation the cloud of points if needed. The center can be found by solving the following system.

$$\begin{cases} \frac{\partial}{\partial C_x} \sum_{i=1}^{n} \left( (x_i - C_x)^2 + (y_i - C_y)^2 - R^2 \right)^2 = 0 \\ \frac{\partial}{\partial C_y} \sum_{i=1}^{n} \left( (x_i - C_x)^2 + (y_i - C_y)^2 - R^2 \right)^2 = 0 \end{cases} \qquad (9)$$

$$\Leftrightarrow \begin{cases} C_x \left( 3\mu_{20} + \mu_{02} - R^2 \right) + C_x^3 + C_x C_y^2 + C_y \left( 2\mu_{11} \right) \\ \qquad\qquad\qquad\qquad = \mu_{30} + \mu_{12} \\ C_x \left( 2\mu_{11} \right) + C_y^3 + C_x^2 C_y + C_y \left( 3\mu_{02} + \mu_{20} - R^2 \right) \\ \qquad\qquad\qquad\qquad = \mu_{03} + \mu_{21} \end{cases}$$

At first sight, solving this system is difficult because the equations are of the third order. Let's assume that the distance between the gravity center of the cloud and the center of the circle is known, that is $C_x^2 + C_y^2 = \Delta$, and using Cramer's rule,

$$\Leftrightarrow \begin{cases} C_x = \frac{(\mu_{30}+\mu_{12})(3\mu_{02}+\mu_{20}-R^2+\Delta)-(\mu_{03}+\mu_{21})(2\mu_{11})}{(3\mu_{20}+\mu_{02}-R^2+\Delta)(3\mu_{02}+\mu_{20}-R^2+\Delta)-4\mu_{11}^2} \\ C_y = \frac{(\mu_{03}+\mu_{21})(3\mu_{20}+\mu_{02}-R^2+\Delta)-(\mu_{30}+\mu_{12})(2\mu_{11})}{(3\mu_{20}+\mu_{02}-R^2+\Delta)(3\mu_{02}+\mu_{20}-R^2+\Delta)-4\mu_{11}^2} \end{cases}$$

Of course, the value of $\Delta$ has to be determined. This can be done by checking that $C_x^2 + C_y^2 = \Delta$ as assumed. With a few simple algebraic manipulations, one can check that $\Delta$ is a root of a fifth order polynomial

$$\Delta^5 + k_4\Delta^4 + k_3\Delta^3 + k_2\Delta^2 + k_1\Delta + k_0 = 0 \qquad (10)$$

The values of $k_0$, $k_1$, $k_2$, $k_3$, and $k_4$ are not given here due to a lack of space, but can be easily computed. There are at most 5 solutions, and selecting the best one can be done using Kåsa's criterion. Only the positive roots should be considered, as $\Delta$ is positive by definition. Note also that there exists always at least one solution, even if the sample points are collinear, because $k_0 \leq 0$[1].

*3) The methods of* Pratt *and* Taubin*:* Instead of parametrizing a circle with $\{C_x, C_y, R\}$, Pratt [14] proposed to use $\{A, B, C, D\}$ such that the equation of the circle is

$$A \left( x^2 + y^2 \right) + Bx + Cy + D = 0 \qquad (11)$$

This parameterization allows to describe circles as well as lines (with $A = 0$). In some cases, only a small arc of the circle is observed and it is hazardous to estimate the radius and to decide on which side of the cloud the circle is. In those cases, some people (*e.g.* [12]) prefer to fit a line instead of a circle. The criterion related to this parameterization is

$$\min \sum_{i=1}^{n} \left( A \left( x_i^2 + y_i^2 \right) + Bx_i + Cy_i + D \right)^2 \qquad (12)$$

Because the parameters $\{A, B, C, D\}$ are defined up a scale factor, and to avoid the trivial solution $A = B = C = D = 0$, one has to add a constraint. It can be showed that Kåsa's criterion is equivalent to this one with the constraint $A = 1$. Pratt [14] used the constraint $B^2 + C^2 - 4AD = 1$ which has the advantage of ensuring that $B^2 + C^2 - 4AD > 0$ (this is required for circles). Taubin [15] proposed

$$\frac{4A}{n} \sum_{i=1}^{n} \left( A \left( x_i^2 + y_i^2 \right) + Bx_i + Cy_i + D \right)$$
$$+ \left( B^2 + C^2 - 4AD \right) = 1 \quad (13)$$

Other constraints have also be proposed by Gander [16] and Nievergelt [17], but we will not consider them in this paper.

## C. Selection of the circle fitting method

We evaluated the four above-mentionned methods (Kåsa, Kåsa with $R$ known, Taubin, and Pratt) by simulation. For the methods of Pratt and Taubin, we have used the publicly available implementation of the author of [12][2].

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[1]The polynomial takes a negative value for $\beta = 0$, and a positive infinite one for $\beta = +\infty$. Therefore, there is at least one root between 0 and $+\infty$.
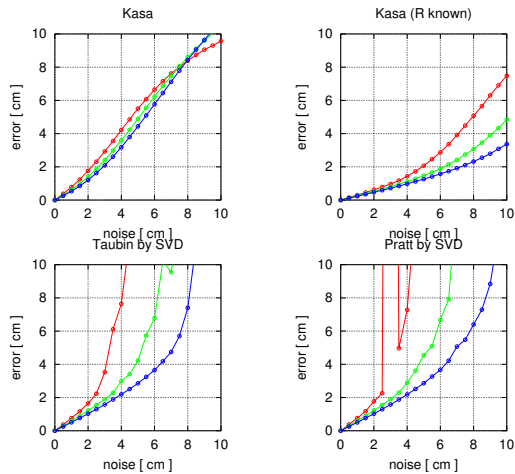[2]http://www.math.uab.edu/~chernov/cl/MATLABcircle.html

Figure 2.   The mean distance between the estimated center of the calibration cylinder and its true center, as a function of the noise level $u$. The red, green, and blue curves correspond respectively to a calibration cylinder with a diameter of $30\,cm$, $40\,cm$, and $50\,cm$. These results show that the fit method introduced in this paper (solving KÅSA's criterion with $R$ known) outperforms the other ones (the methods of KÅSA, TAUBIN and PRATT).

A cylinder is placed randomly, and fully included in the visual field of the sensor. It is separated from the sensor by a distance between $50\,cm$ and $10\,m$. A noise was simulated on the distances measured by the virtual sensor: each measurement is corrupted independently of the others, and the noise is distributed uniformly on the $[-u, u]$ interval. Therefore, we assume that the distance measures are unbiased. We observe the mean error, *i.e.* the mean distance between the estimated center of the calibration cylinder and its true center. We want to select the fitting method with the lower mean error. The mean error depending on the noise level is depicted in Figure 2.

Note that KÅSA's method is known to be highly biased when a small arc is sampled. This bias is difficult to compensate, because it depends on the noise level, and the sensors are insufficiently characterized to predict the noise level.

Our experiments have shown that KÅSA with $R$ known is the fitting method that is best suited to our particular case. KÅSA with $R$ known is less sensitive to noise than KÅSA. The methods of PRATT and TAUBIN are almost equivalent, and are unable to cope with important noise (whether one uses a SVD or Newton's method). The reason is probably that fitting lines as well as circles in a bad idea in our case because $C_x = -\frac{B}{2A}$ and $C_y = -\frac{C}{2A}$. Therefore, if the fitting method prefers a line, estimating $C_x$ and $C_y$ is impossible since $A = 0$. This conclusion stands in deep contrast with the one of [12], which stated that the methods PRATT and TAUBIN are theoretically preferable to KÅSA's one, as a general rule.

### D. Remark: application to robotics

Fitting circles of known radius to points sampled along a small arc is a problem often encountered in robotics. For example, in [18], a mobile robot should interact with known objects that have a cylindrical base. The sensor is a range laser scanner or a 3D camera, and therefore the localization of the objects is equivalent to the estimation of the object center from
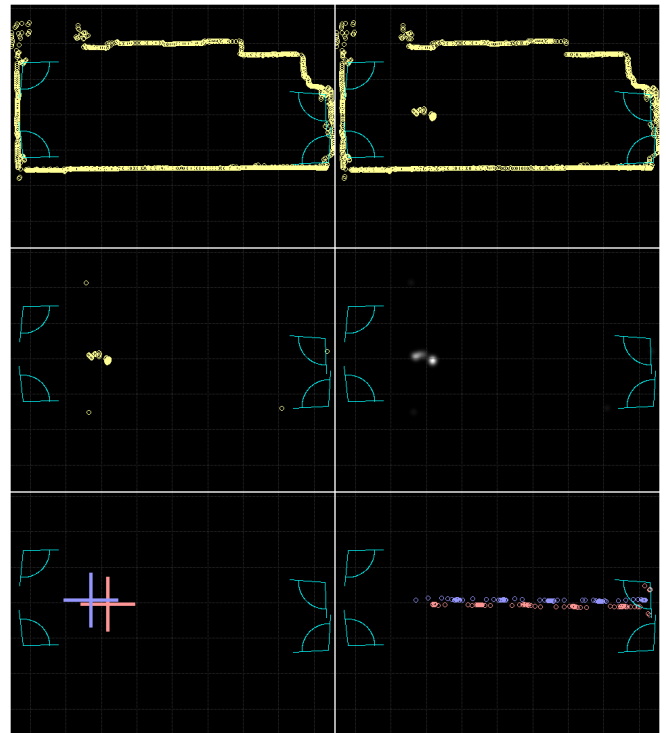


Figure 3.   The different steps of our method. From the top left picture to the bottom right one: (1) the model of the empty scene, *i.e.* the background (2) the points seen by all sensors (3) the result of the background subtraction (4) after the convolution with a gaussian kernel (5) after local maxima search (6) the final result of the tracker.

a set of points sampled along an arc of circle. This is exactly the same problem we are facing here. In [18] the circle is fitted with KÅSA's method; we know now that it is not the best choice and that using KÅSA's criterion with $R$ known would be a lot more precise.

### IV. THE FEET TRACKER

The most straightforward methodology to track the feet consists in building a localization map (*cf* [10]), filtering uninteresting static objects (chairs, tables, …) by using a background subtraction algorithm (such as [19]), and isolating the feet by a connected components analysis (such as [20]). However, the technique proposed in [10] to combine the information provided by several range laser scanners assumes that the observed scene is nearly static, and that the sensors don't see outlier points. Unfortunately, this is not the case, so we propose a new method. Its main steps are depicted in Figure 3.

### A. Locating the feet

Each sensor sees a cloud of points in the horizontal plane. Thanks to the calibration, these clouds can be superimposed, and merged. From the resulting cloud, we have to estimate a set of two points that are the centers of each foot (or leg).

We apply a background subtraction to the signal provided by each sensor, in order to filter out the static elements of the scene and to keep only the points corresponding to the

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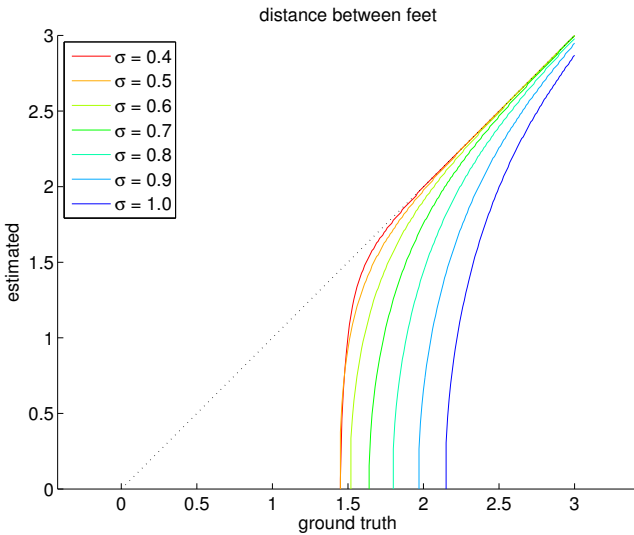
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Figure 4. The theoretical error on the feet positions. The unit chosen to express the distances and $\sigma$ is such that the diameter of the leg is $D = 1$. These curves have been obtained by simulation in noise-free conditions, with uniform and dense sampling.

feet. Then, the remaining points are convolved with a gaussian kernel of standard deviation $\sigma$ (*i.e.* a gaussian is placed at each each point, and they are summed). We expect to have, in most cases, the two largest local maxima where the feet are. We do not provide any output if there is less than two local maxima, or if they are spaced more than it is possible. This method is robust to outliers, and therefore a simple background subtraction method suffices.

The standard deviation $\sigma$ is the only parameter that has to be chosen. For the sake of theory, let's assume that the horizontal section of the feet are circles, and that they are uniformly sampled. Let's denote $D$ the diameter of the feet.

We want to get a local maximum per foot. If there was only one foot in the scene, it can be showed that $\sigma$ should be larger than $\frac{D}{2}$ if the sensors see only two points of the feet, or larger than $0.36\,D$ if the sensors see a lot of points. Now, consider two feet. If $\sigma$ is too large, there is a risk to observe only one maximum for both feet. The fact that we observe one or two maxima depends on the distance between the feet, on $D$ and on $\sigma$. This relation is depicted in Figure 4. We consider that, in the worst case, $D = 14\,cm$ (with trousers) and that only two points are seen by foot. Accordingly, we chose $\sigma = \frac{D}{2} = 7\,cm$. According to Figure 4, we expect our localization procedure to fail if the distance between the centers of the legs is less than $14 \times 1.4428 \simeq 20\,cm$ and to give a biased result if the distance is less than $14 \times 2 \simeq 28\,cm$.

In future work, we would like to improve the localization procedure in order to obtain an unbiased feet position estimate, and to be able to localize the feet even if there are close. Some ideas are (i) to correct the estimate thanks to the known relation between the estimated inter-feet distance and its true value, or (ii) to use a gaussian ring kernel instead of the gaussian one, or (iii) to use machine learning principles.
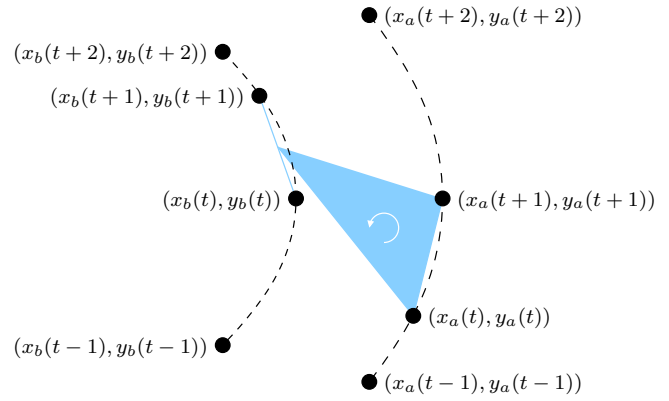


Figure 5. $\Phi_{ab}(t)$ is the signed area of the blue triangle.

### B. Tracking the feet

At this point, we have a couple of points at each frame. In this step, we would like to cluster all the points in two classes, in order to obtain a trajectory for each foot.

At the time this paper is written, we minimize the total length of the two trajectories. This criterion leads to excellent results when the observed person walks along a line. However, from time to time we observed that when the person turns quickly, the trajectories may cross. This is probably due to an insufficient acquisition rate ($15\,Hz$). This kind of problem also arises with a tandem gait walk. In future work, we plan to improve the technique used to track the feet, perhaps using a Kalman filter.

### C. Identifying the feet

We know the position of both feet over time, but we still need to determine which foot is the left one, and which one is the right one. The only clue available is the motion direction. Therefore, it is impossible to correctly identify the feet if the observed person moves in reverse. Let's denote $(x_f(t), y_f(t))$ the coordinates of the foot "f" at time $t$. The following quantity

$$\Phi_{ab}(t) = \frac{1}{2} \begin{vmatrix} x_a(t) & x_a(t+1) & \frac{x_b(t)+x_b(t+1)}{2} \\ y_a(t) & y_a(t+1) & \frac{y_b(t)+y_b(t+1)}{2} \\ 1 & 1 & 1 \end{vmatrix} \quad (14)$$

is positive if the foot "$a$" is on the right of the foot "$b$" between the times $t$ and $t+1$, and $|\Phi_{ab}(t)|$ is a certainty factor (the geometrical meaning of $\Phi_{ab}(t)$ is depicted in Figure 5). Therefore, letting $T$ be the total walk duration,

$$\sum_{t=0}^{T-2} \left[\Phi_{12}(t) - \Phi_{21}(t)\right] < 0 \quad (15)$$

if the trajectory number 1 corresponds to the left foot. We expect this criterion to be suitable, not only for straight paths, but also for any path (such as an ∘-shaped path or an ∞-shaped path).

### V. APPLICATION TO NEUROLOGICAL DISEASE ANALYSIS

Gait disorders measurement and quantification is of the utmost importance in the follow-up and therapeutic decision-making process of numerous medical conditions (whether
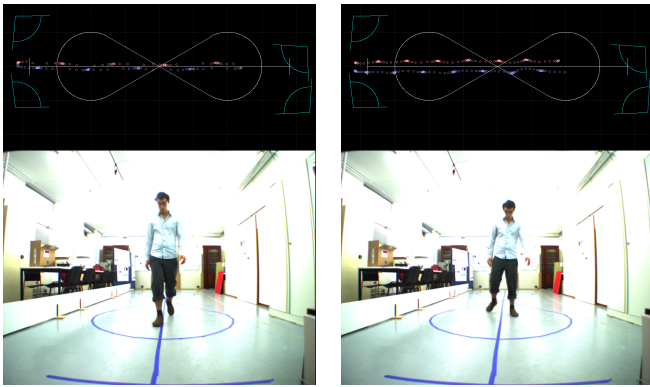
S. Piérard, M. Van Droogenbroeck, R. Phan-Ba, and S. Belachew. **A new low-cost and non-intrusive feet tracker**. In *Workshop on Circuits, Systems and Signal Processing (ProRISC)*, Veldhoven, The Netherlands, November 2011.

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Figure 6. Screenshots of our software. Upper images display the position of the four sensors (obtained by calibration), a $25\,ft$ straight path, and the previously estimated feet positions. On the left hand side, the observed person has a normal gait, and on the right hand side, he has an ataxic gait. Such pathologies can be easily detected and measured with our method. A few full videos are available at http://www.ulg.ac.be/telecom/vgaims/.

orthopaedic, rhumatologic, pediatric, cardiorespiratory, or neurologic). For example, in the field of multiple sclerosis, a common neurological disease where gait is frequently impaired, change in walking performances can lead to significative therapeutic modifications [21].

However, the current available tools measuring gait dysfunction suffer from various limitations [22] and are completely blind to certain important gait features, such as ataxia, symmetry of the feet paths and individual feet walking speed, freezing of gait, etc, that are only qualitatively described in the neurological examination. The feet tracker developed in this work allows one to easily capture these features in a simple way, and at low cost (see Figure 6).

A dozen of videos demonstrating our results are available at http://www.ulg.ac.be/telecom/vgaims/. Qualitatively, our method is robust and precise. It is clear beyond the traditional measurement of global walking speed, and its use can be extended to measure more subtle and specific gait abnormalities. However, the questions of precision and accuracy are still problematic, because of the intrinsic lack of ground-truth data in this specific field.

## VI. Conclusion

We have developed a new platform to capture gait, and a dedicated calibration procedure. It is a non-intrusive and low-cost platform. It has proven to be suitable for medical purposes, and we think that it can be used for other applications like automatic person identification.

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