Assessment of perceptive accuracy for motor performance in persons with multiple sclerosis

Introduction

The majority of people with multiple sclerosis (PwMS) have impaired gait and sit-to-stand function: they walk slower, with an increased energetic cost of walking and cluster-specific alterations from the physiological gait pattern, while lower limb extensor weakness and diminished postural control have also an impact on their sit-to-stand performance. (1-4)
After sustained activity these impairments tend to increase for a large part of PwMS: motor performance fatiguability, the objectively measured acute performance deterioration, may involve both quantitative and qualitative aspects of their motor performance. (5, 6)
This can be a barrier to participation in leisure-time physical activity (PA), creating a vicious circle leading to increase in disability: inactive PwMS walk slower with an increased energetic cost of walking, consequently experiencing more reductions in walking bouts quality and distance in their daily life.
Furthermore, motor performance impairments and levels of PA, in this population, may also be linked to sensory abnormalities, personal beliefs and fluctuations of symptom intensity. (7-11)
Fatigue is the hallmark symptom in MS, with reported prevalence reaching 78%, and PwMS with higher levels of perceived fatigue tend to become less physically active in their daily life, also in absence of motor performance fatiguability. (12, 13)
Generally, fatigue is a sense of tiredness and lack of energy that can interfere with a person's usual daily activities and, leading to increase the weighting of effort costs in cost-benefit evaluations, it can be a functional interoceptive signal to stop of modify our activity, take appropriate rests or pace our efforts. (14)

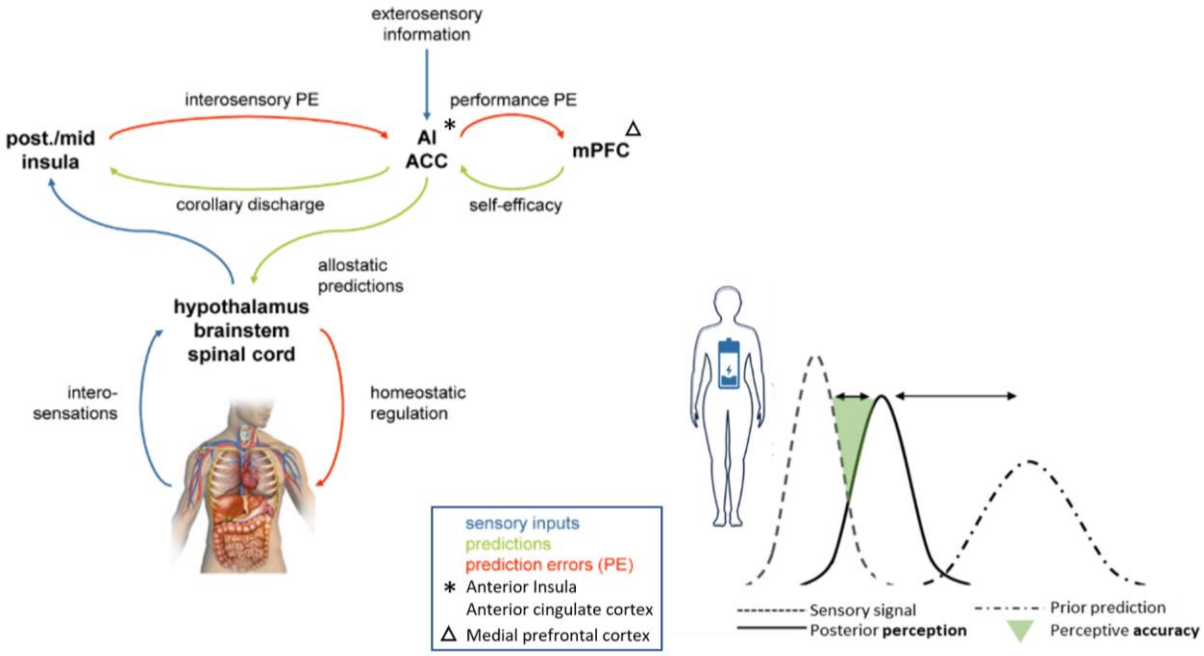


Figure 1 The predictive model of bodily states. Illustration of the interoceptive core control network and of the precision weighted inferential process forming perception. Adapted from (15)

The efficiency of this self-regulation system depends on the ability of the central interoceptive core control network to accurately judge our body state (which resources are available versus necessary to achieve a desired outcome) and, when carrying out physical activity, to timely produce allostatic adjustments (i.e. 'actions to maintain the body in homeostasis') through interactions with the

autonomous nervous system: rebalancing its activity, with a shift from energy saving to energy expenditure. The perception of the body homeostatic state is constantly updated through an inferential process: there is always a self-generated prior prediction confronted with the actual sensory signal, in a precision weighted manner (see Figure 1).
Therefore, potential sustained input signaling a diagnosis of low allostatic performance (i.e. chronic interoceptive surprise= persistent inaccuracy of prior predictions) can give raise to the perception of fatigue as 'lack of control over body states', in this framework located at a metacognitive level. (15-17)
During goal-directed motor performance the brain relies on interoceptive, exteroceptive and proprioceptive signals to gauge the ongoing performance: all these sensory signals have to be integrated and, with multiple sclerosis, this process can be affected by the neuropathology and the prior beliefs may therefore dominate the perception, lowering their perceptive accuracy.
It can become harder for some PwMS to adapt to new experiences, with the risk of maladaptive changes in the way they carry out daily life activities and in the participation in physical activity: possibly hypoactivity due to underestimation of true physical capacity, or hyperactivity in the opposite case. (18, 19)
Keeping in account that perception (and its accuracy) may vary in time, for different body-parts and for different activities, it is important to have an holistic and task-relevant approach to its assessment. In this view, perception is a multifaceted ability which can be studied at different levels, forming separate dimensions:

- Accuracy, degree of truthfulness of perception compared to performance
- Attention, degree of attention for perceptive cues
- Sensibility, self-beliefs over one's own perceptive accuracy and attention
- Awareness, correspondence between measured (objective) and reported (subjective) dimensions

These dimensions can be quantified specifically, with different methods and for different organ systems ('body axis'), in various experimental tasks of perceptual discrimination or correspondence. (20-22)

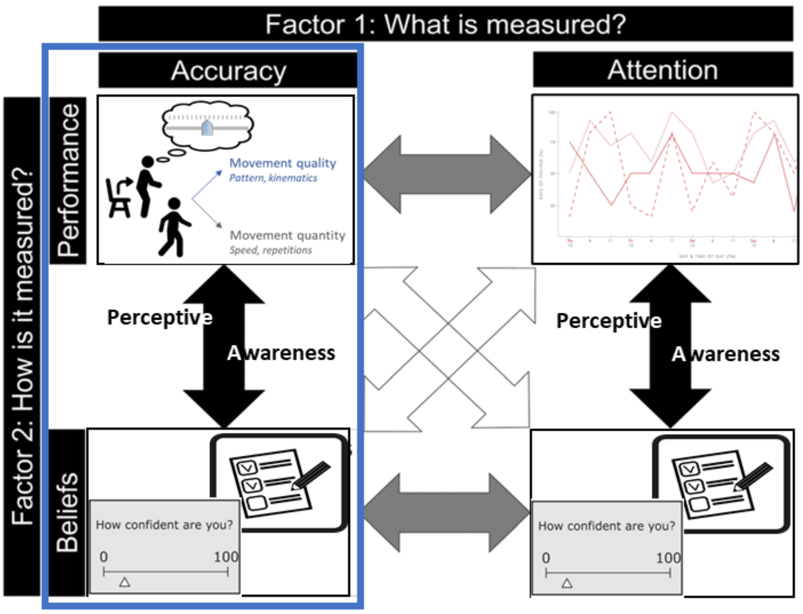


Figure 2 Framework of perceptive abilities assessment. In the present study we will measure objective and subjective perceptive accuracy for motor task-performance. Adapted from (Murphy et al., 2019)

The aim of this study is to characterize perceptive abilities in PwMS compared to controls when performing prolonged functional tasks such as walking and repeated standing from a seated position.

Methodology

Participants

44 PwMS and 44 healthy controls (40, +10% to cover possible dropouts and missing data) will be recruited from the Flemish MS rehabilitation centers in Melsbroek (NMSC) and Pelt (Noorderhart RMSC), and as well from the REVAL research center in UHasselt and its established network (eg. UMSC Patient Platform). Information flyers will be distributed in the centers and online content via the website and social media of REVAL and the Flemish MS society; no economical compensation will be provided by the research organization to the participants of this study. We will search age and sex-matching subjects for the healthy controls, considering a 5-year range per subject. After giving informed consent, demographics of age and gender, height and weight, years of education, as well as MS-related information such as EDSS, type of MS, use of assistive device for walking in daily life, and years since diagnosis, will be collected and provided by the centers or via self-report. The participants will be instructed to keep their normal routine but to avoid extraneous physical activity at least 24 hours before the data collection session.

- Inclusion criteria for PwMS: age between 18 and 65 years old; a diagnosis of MS (2017 revisions of the McDonalds criteria); ability to walk for 6 minutes without rest and without the need of a walking aid; ability to repeatedly perform the sit to stand transitions on a standard chair (43cm seat height) without hand support. Additionally, no relapses >1 month preceding the start of the study.

- Inclusion criteria for healthy controls: age between 18 and 70 years old, sex- and age-matched on a group level.

- Exclusion criteria: cognitive impairment hindering understanding of study instructions, pregnancy, and musculoskeletal disorders in the lower limbs (not related to MS), cardiovascular red flags for exercise (screened with Physical Activity Readines Questionnaire), other diagnosis for neurological or metabolic disease limiting the full execution of the tests (eg. peripheral neuropathy altering the foot plantar sensibility).

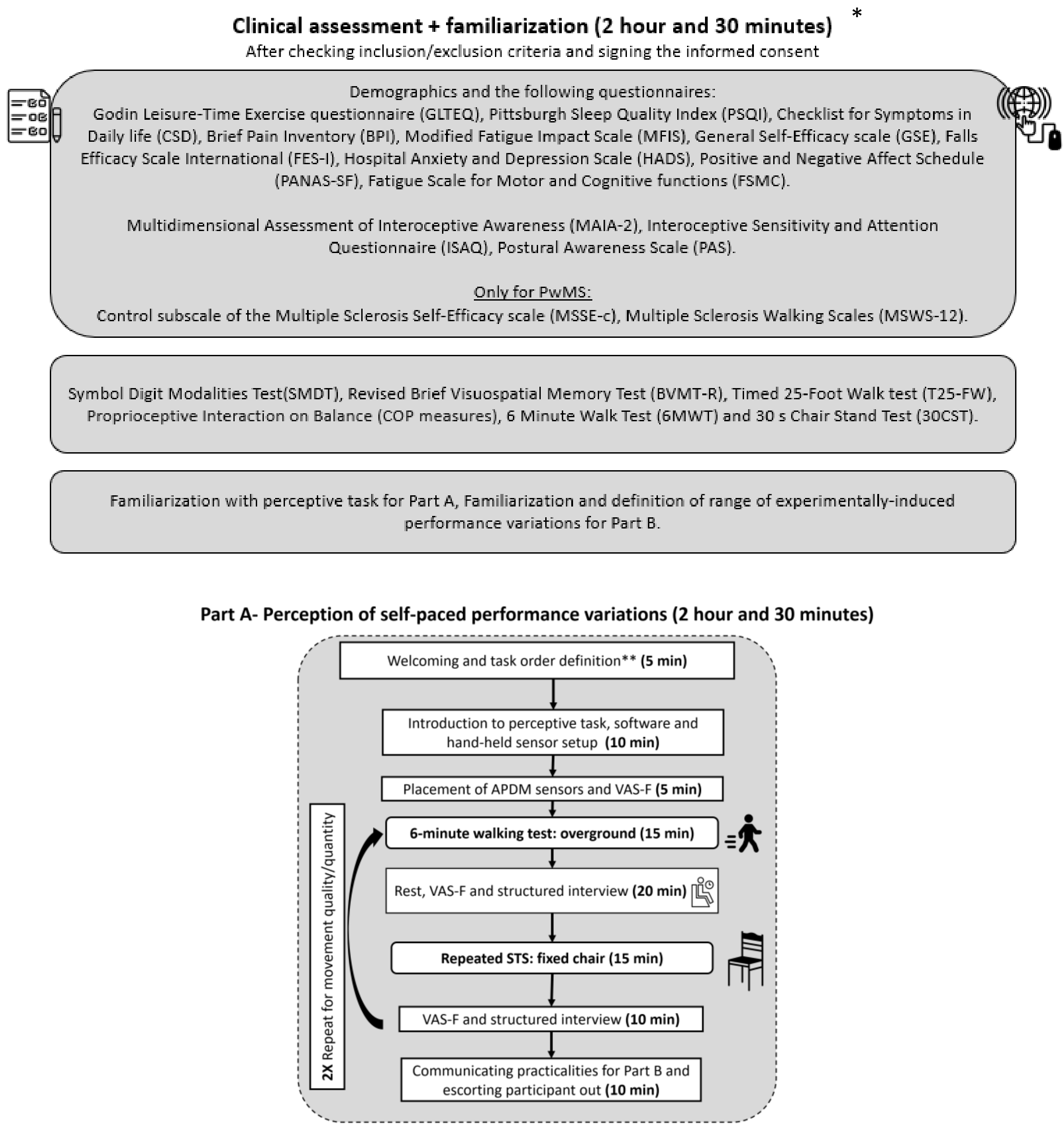
Inclusion/exclusion criteria will be controlled at the beginning of the first session: the participant will read the criteria presented in the informed consent and will be asked to confirm that he/she can enroll in the study.

In particular cardiovascular red flags for increase in physical activity will be screened with the Physical Activity Readines Questionnaire, a self-assessment tool including 7 questions. In case of a positive response to one of the questions the participant will be directed to consult his/her physician before enrolling in the study.

Finally, in case of a female participant unsure about her pregnancy state we will offer a free pregnancy test to control for it before enrolling in the study.

Experiment outline

This is an exploratory observational study with experimental tasks to measure perceptive accuracy for motor performance in people with multiple sclerosis and healthy matched controls. This study proposes primary and secondary research questions which will be tested in the contest of two different motor tasks, namely walking and sit to stand, and will be performed in two or three days: in case the participant could complete the questionnaires at home, via the provided web service (Castor®) the first and second sessions can be efficiently merged in one, reducing time demand and travelling costs for the participant. The first day (Clinical assessment and familiarization) serves to obtain a characterization of participants, and it will include familiarization sessions, to ensure that the participants understand the instructions and can cope with all the motor and perceptive tasks. On the second day (Part A) the self-paced performance variations protocols will be performed twice, with adapted instructions (detect the qualitative or quantitative aspects of motor performance) and counterbalanced order, for each the two studied motor tasks: walking (Task 1) and sit to stand (Task 2). On the third day (Part B) the experimentally-induced performance variations protocols will be performed for the two studied motor tasks. The study flows with the clinical assessment + familiarization session, parts A and B can be seen in the next page, presented in Figure 3.



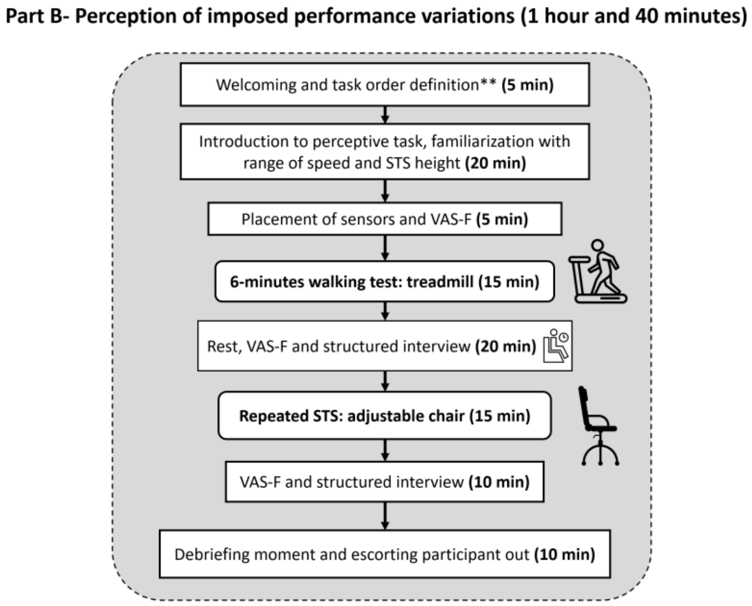


*Figure 3 Experimental outline of the study. *Note that Clinical assessment + Familiarization and Part A can be also on the same day. VAS-F= Visual analogic scale for fatigue, COP= Center of pressure*

Clinical assessment + familiarization

- ### Clinical assessment

The participants will be contacted to verify their interest and eligibility (inclusion and exclusion criteria) to participate in the study. In the case of inclusion in the study, demographic data will be recorded via web-based secured digital surveys (Castor® web application) and filled in by the examinator, including: 'Sex', 'Age', 'Body Mass Index', 'Work status', 'Year from diagnosis' (if living with a chronic condition, specifying the subtype when relevant), 'Use of assistive device for walking in daily life', 'Use of medications' (that could influence fatigue, motor or cognitive performance).

-Questionnaires

Different questionnaires will be handed-out to the participants or, when the online filling modality is preferred by the participant, they will be sent to them in via a secured web link (available via Castor®). We will ask the participant to make this choice when they will be informed about their eligibility in the study.

Part of the questionnaires will serve as screening tools for factors that potentially interfere with the perceptive abilities of the participants: The Godin Leisure-Time Exercise questionnaire (GLTEQ) for the level of physical activity; the Pittsburgh Sleep Quality Index (PSQI) for sleep quality in the last month; the General Self-Efficacy scale (GSE) for self-efficacy beliefs; the Checklist for Symptoms in Daily life (CSD) for self-reported habitual symptom perception; the Brief Pain Inventory (BPI) to measure the severity of pain and its impact on daily functioning; the Falls Efficacy Scale International (FES-I) for the level of concern about falling; the Hospital Anxiety and Depression Scale (HADS) for screening the presence of symptoms of anxiety or depression in the last week; the Positive and Negative Affect Schedule (PANAS-SF) to assess positive and negative affectivity; the Fatigue Scale for Motor and Cognitive Functions (FSMC) for fatigue; the Modified Fatigue Impact Scale (MFIS) for perceived impact of fatigue; and, only for PwMS, the Control subscale of the Multiple Sclerosis Self-Efficacy scale (MSSE-c) for disease specific control beliefs and the Multiple Sclerosis Walking Scales (MSWS-12) for perceived walking ability.

To indagate the participant's subjective beliefs about their perceptive abilities and compare the ones of PwMS to the ones of HC, the Multidimensional Assessment of Interoceptive Awareness (MAIA-2) and the Interoceptive Sensitivity and Attention Questionnaire (ISAQ), that register self-beliefs over interoceptive abilities and the Postural Awareness Scale (PAS), measuring self-beliefs over proprioceptive abilities, will be administered to both groups.

Research questions relative to the reported subjective beliefs about perceptive abilities

- Do PwMS and HC differ in their reported subjective beliefs about perceptive abilities quantified by the MAIA-2, ISAQ and PAS scores and subscores?

Hypothesis

- PwMS differ from HC in their reported subjective beliefs about perceptive abilities: lower interoceptive and postural awareness (MAIA-2 and PAS total score) and higher attention and sensibility (ISAQ total score) is expected in PwMS

-Cognitive and motor performance assessments

For the execution of the cognitive and motor performance tests, participants will be asked to reach the clinic (MS Rehabilitation Center – Noorderhart, Pelt or National MS Center, Melsbroek), or, in case is more convenient for the participants the REVAL research center, to meet the experimenter. A short briefing will serve to ask the participants if they had difficulties in filling the surveys online and check for mistakes or missing answers. Participants will be also asked to wear flat comfortable shoes (mandatory characteristics of shoe's sole: maximal difference between heel and toes sole height= 1 cm) and to carry with them shorts or legging pants for a better fixation of the sensors; they will be required to wear the same clothing for all the different parts of the study.

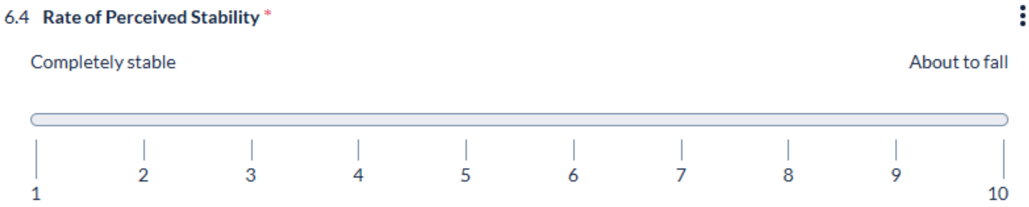
Participants will be tested for cognitive executive functions (ie. information processing speed) via the Symbol Digit Modalities Test (SMDT) if they are not able to provide the result of a recent (<6 months) SMDT. In case the patient is contacted in the MS centers, the clinics will provide the result of the most recently executed SDMT. The SDMT is a timed thinking task that involves associating numbers with symbols. Participants will be asked to provide as many correct numbers as they can within 90 seconds.

Visuospatial memory will be assessed with the Revised Brief Visuospatial Memory Test (BVMT-R). The BVMT-R is a visuospatial memory test, such that participants view a stimulus page for 10 seconds and are asked to draw as many of the figures as possible in their correct location on a separate sheet of paper.

Participants will be instructed to walk as fast as possible to measure their maximal walking speed with the Timed 25-Foot Walk test (T25-FW). The test will be performed with a flying start, it will be repeated two times and the average time of the two trials be used as the final performance.

The Test for the Sensory Interaction of Balance will be used to define the proprioceptive interaction on balance: force plates will measure center of pressure (COP) displacement in response to standing on a stable and unstable support surface (standard foam pad), with eyes open and closed. The degree of increase in COP displacement when applying the foam represent the proprioception quotient (i.e. reliance of body balance on the proprioceptive system). (23)

After each of the four conditions of the Test for the Sensory Interaction of Balance the participant will be asked for a Rate of Perceived Stability, a 1-10 visual analogical scale to rate balance challenge.(24)



Afterwards, the participants will perform the 6 Minute Walk Test (6MWT), walking back and forth in a 30m corridor as fast and safe as possible for 6 minutes, the 30 seconds Chair Stand Test (30CST), repeating STS transitions as fast and safe as possible for 30 seconds, and the Dual Joint Position Test (DJPT), a test for proprioception. (25)

Except for the T25FW, the participant will wear wearable sensors in pre-defined body positions for the gait and STS tests (6 OPALs – APDM technology© IMU sensors: 2 over the dorsal part of the feet, 2 on the lower legs, 1 anterior to the sternum and 1 posterior to the third/fourth lumbar vertebra; 1 Polar H10 chest-band for real-time heart rate monitor).

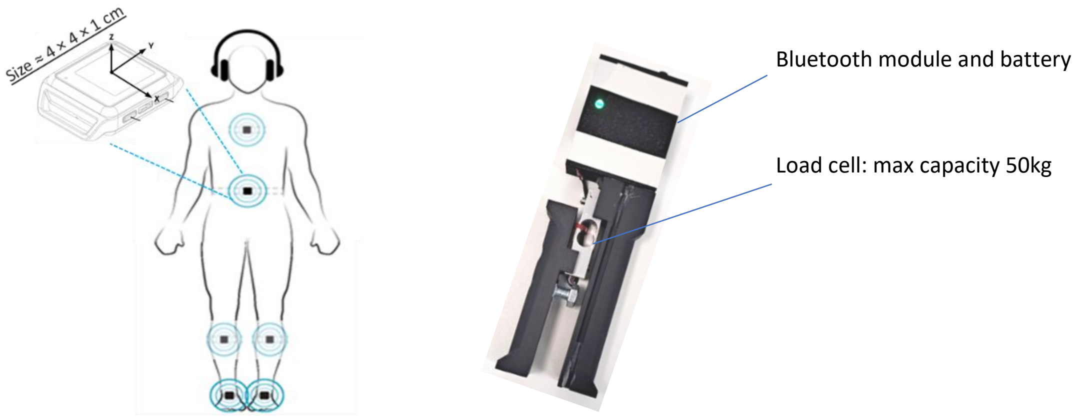


Figure 4 Wearable sensors placement on the body and working prototype of the force sensing device for perceptive tasks

The perceived fatigue will be asked just before and immediately after the 6MWT and the 30CST using the VAS-F, a 0-10 visual analogical scale for state fatigue.

not at all **fatigued**	0	1	2	3	4	5	6	7	8	9	10	extremely **fatigued**

Figure 5 10 points visual analogic scale for fatigue (VAS-F)

- **Familiarization with motor and perceptive tasks**

At this point the participant will be familiarized with the experimental procedures and the experimenter is defining the ranges of performance variations that will be experimentally-induced in part B. This will happen in the presented order:

Familiarization with perceptive task for Part A – 'Perception of self-paced performance variations'

A perception reporting familiarization procedure will ensure that the participants understand the instruments and methods utilized by the experimenter to register their subjective reports on their ongoing motor performance. The participant will be equipped with noise-cancelling headphones and an hand-held force sensing device, shaped in a similar fashion as the Jamar hand-dynamometer®: instructors will explain that the device will be utilized during motor tasks like walking and sit to stand for recording the time-point of any perceived changes in their own motor performance (in 'gait speed or smoothness' during a 6MWT or in 'sit-to-stand duration or smoothness' during repeated STS postural transitions). The threshold sensitivity of the sensor (ie. the minimum value of input hand-grip force to save a report) will be set at 25% of the maximal hand-grip strength of the participant (average of three maximal isometric hand-grip test, measured with the same sensor). Trials are executed with the use of simple perception tasks (eg. reacting to visual stimuli while walking or doing STS repetitions) and the participant is informed that he will be following these same instructions to report his own perception about unspecified aspects of their motor performance during walking and STS in the experimental Part A of the study.

Range of imposed performance variations (part B) – Treadmill walking

A treadmill familiarization procedure will ensure that every participant is enrollable to perform experimental part B. The subjects will be asked about previous experiences with treadmill training/use and this will be noted down in the participant file: participants will undergo 10 minutes of treadmill walking with the supervision of a physiotherapist to familiarize with the moving belt, position and use of safety bars and other general safety and usability issues.

A speed-range definition procedure will permit the quantification of the appropriate personalized range of experimentally-induced performance variations for every participant. All the participants will start walking on the treadmill at 50% of their *maximal treadmill walking speed* (speed calculated from their overground performance in 6MWT: maximal speed maintained for at least 15 seconds during the test) and they will be asked to confirm if that is their *comfortable treadmill walking speed*; if this is not the case the experimenter will adjust the speed based on the participant's subjective reports and, finally, will let them walking at that constant speed for one minute.

Immediately after the selection of their *comfortable treadmill walking speed* (i.e. during the one minute of constant speed walking) the participants will be instructed to maintain their position on the treadmill, in the antero-posterior direction, adapting their gait to the belt continuous acceleration toward their maximal walking speed (selected from their overground performance in 6MWT, see paragraph above). This speed range, will be used as personalized range of experimentally-induced performance variations (in Part B).

Range of imposed performance variations (part B) – Sit to stand

A STS seat height range definition procedure will permit the quantification of the appropriate personalized range of experimentally-induced performance variations for every participant. The 30CST requires the maximal frequency of STS transitions to be produced by the subjects on a standardized chair (fixed seat height of 43.2 cm), exposing them to incremental challenges due to physical exertion over a short time. In our study the baseline seat height will be normalized on the physical characteristic of the participants (=100% of the distance from the ground to the inferior margin of the patellar bone, measured in sitting, including the height of the shoes sole, wearing the same shoes as in all the other experimental parts and after ensuring vertical alignment of the tibia). The STS seat height range that will be used as personalized range of experimentally-imposed performance variations (in Part B) will be then calculated as: baseline seat height ± 20% (from comfortable to lowest seat height, see 'verbal descriptors' below.

Familiarization with perceptive task for Part B – 'Perception of imposed performance variations'

At this point the experimenter will present two vertical visual scale on a screen, ranging from 0 to +100 or from 0 to -100, which have been designed to match the participants' perception of ongoing motor performance, either for treadmill walking or STS.

Verbal descriptors will be positioned on the right side of the scale at every 10th step describing different levels of walking speed or STS difficulty level. Note (see below) that the verbal descriptors of the two visual scales will be inversely directed, but that 'minimal seat height' represent the most difficult condition in the STS task and therefore correctly occupies the upper limit of the scale.

<u>Perceived treadmill speed scale</u> 0% =your comfortable speed; +100% =your maximal speed

<u>Perceived seat-height scale </u>0% =your comfortable seat height; -100% = your minimal seat height

Experimental design Part A: 'Perception of self-paced performance variations'

During Part A the participants will perform the experimental tasks (first the 6 minutes of walking and then the STS repetitions) of perceptive detection twice, with different instructions driving their attention on their performance quantity- or quality- variations: the order of the participant's execution of the two pair of experimental tasks will be counterbalanced at group level to mitigate any potential bias or effects that might arise from the order in which the tasks and relative instructions are presented.

Task 1: Perceptive accuracy for walking speed variations during overground 6MWT

The participants will be tested overground, during a 6MWT, for their ability of accurately perceive changes in their self-paced gait speed: they will be instructed to walk for 6 minutes at the maximal speed that they can maintain safely and reporting any perceived oscillation in their own speed by squeezing the handheld sensor. The reason for the selected modality to acquire patient reports is that holding the sensor in the hand can serve as a reminder for the ongoing perceptive task, ensuring a continuous attention toward their speed and acquisition of reports (the action of holding the sensor, without squeezing it, confirms that the participant is not perceiving any change in speed, accordingly to the received standardized instructions).

Neutral instructions will be provided to the subject before starting the 6MWT by reading the following script: "When you will hear the beep tone, squeeze the sensor and start walking at the maximal speed that you can maintain safely for the 6 minutes-length of the experiment. During this period, but only for the straight parts of the walking track, please pay attention to your walking speed. Natural variations in your walking speed may occur during the test. We want you to notice, and report them using the handheld sensor being them accelerations or decelerations, this information does not matter for our test and therefore you will not have to indicate it: as soon as you perceive a change in your walking speed, squeeze the sensor in your hand to save your report. Report only changes in speed that you perceived during the straight parts of the walking tract: all the variations that are due to the turning will be cut out from the analysis. If you will squeeze during a turn, that report will be saved as if it was given three steps before the turn.

Participants will be also equipped with noise-cancelling headphones to avoid auditory perception of steps rhythm and influence of possible environmental distractions. Using wearable sensors to detect motor performance (spatiotemporal and kinematic parameter detected with a configuration of 6 OPALs – technology© IMU sensors: 2 over the dorsal part of the feet, 2 on the lower legs, 1 anterior to the sternum and 1 posterior to the third/fourth lumbar vertebra, see figure 4) will allow us to then compare the time and frequency of the reports with the actual speed variations, cutting out the steps executed while turning, and propose novel outcome measures: the change in speed at the first report as a perceptive threshold for overground walking speed changes, informing on the minimal clinically important change, and the ratio between reporting frequency and actual speed variability, reflecting perceptive accuracy (see example plot in Figure 6).

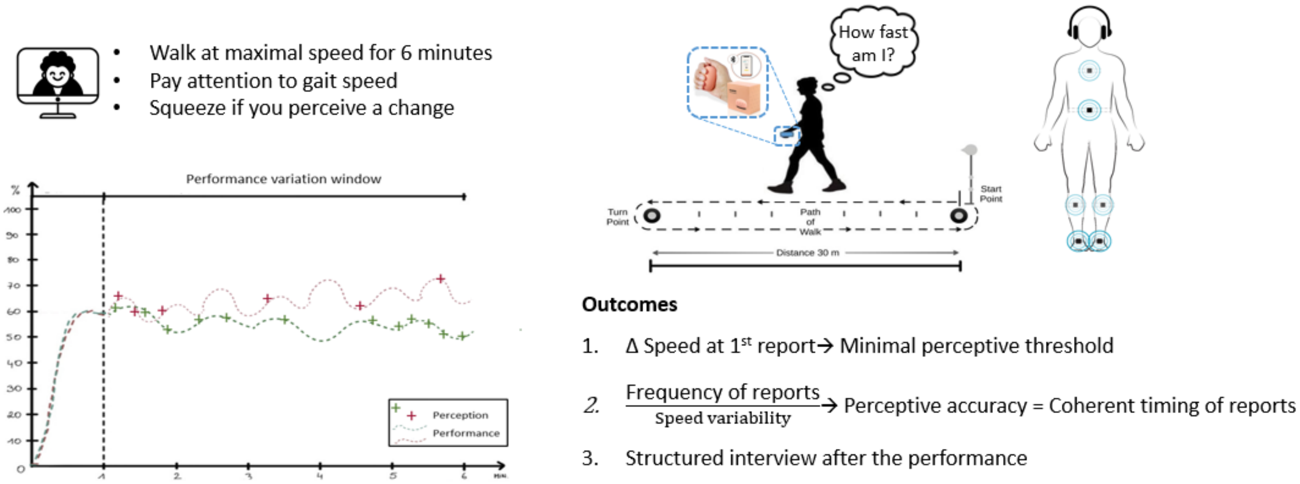


Figure 6 Perceptive accuracy for walking speed variations during overground 6MWT: Task 1 illustration, wearables placement and Perception vs Performance plot graphic illustration

The intensity of perceived fatigue will be asked just before and immediately after the test using the VAS-F (see Figure 4). Furthermore, a short structured interview will follow including the following question: “On a scale from 0 to 100, how certain are you that you have been precise/accurate in detecting ongoing variations in your performance? Please mark your confidence level on the presented visual scale”. This question is then followed by an open-ended question where the participant is asked to report on which sensory information he/she was relying to gauge performance variations and give the reports: “On which aspects of your motor performance where you paying attention to detect variations and decide to give a report during the task? Please list them here”.

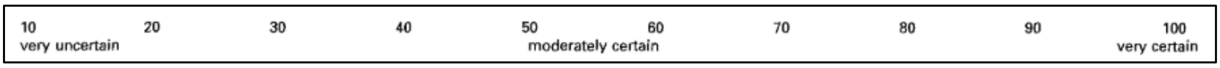


Figure 7 Visual scale for confidence rating: subjective beliefs on their perceptive accuracy

Task 2: Perceptive accuracy for STS duration variations during repeated STS postural transitions

The participants will be tested on a armless chair of normalized seat height, for their ability to accurately perceive changes in their self-paced sit to stand duration.

They will be instructed to perform STS repetitions at a fixed pace, but to execute each transition from sitting to standing as fast as possible. Sitting with the back rested on the back-support will be the starting position of the test. After the first STS transition (i.e. starting from the first standing position), they will be presented with a countdown of 10 seconds during which they must return to the sitting position and, from that position, perform the following STS transition. The participant will be asked to use the time in between STS repetitions to evaluate their sit-to-stand duration, comparing it with the previous, and decide if to report (or not) a change in STS duration (using the same handheld sensor as during the 6MWT). The STS execution will be stopped by the examinator after 36 repetitions.

Neutral instructions will be provided to the subject before starting the STS test by reading the following script: “When you will hear the beep tone, squeeze the sensor and start performing sit-to-stand repetitions, doing each of them standing up at the maximal speed that you can use to stand up safely. Be aware that we are not asking you to perform as many repetitions you can in a limited amount of time, butthat you will be asked to stand up from the chair once every 10 seconds, you just have to do each repetition at your maximal speed: going from sitting to standing as fast as you can. Natural variations in your sit-to-stand speed may occur between repetitions. We want you to notice and, starting from the second repetition, report them using the handheld sensor: if you perceived a change in the time needed to stand up, being it shorter or longer does not matter (you will not have to indicate it), squeeze the sensor in your hand during the resting phase .In between repetitions you will have 10 seconds to decide if to report a change: in the case you didn’t notice any change, simply don’t squeeze.”

Participants will be also equipped with headphones. Using the same set of wearable sensors, as in task 1 (6MWT overground), to detect motor performance will allow us to then confront the time and frequency of the reports with the actual STS duration variations, and propose novel outcome measures: a perceptive threshold for STS duration changes and the ratio between reporting frequency and actual STS duration variability, reflecting perceptive accuracy (see example plot from piloting in Figure 8). The intensity of perceived fatigue and a short structured interview will follow in the same way as in task 1 (6MWT overground).

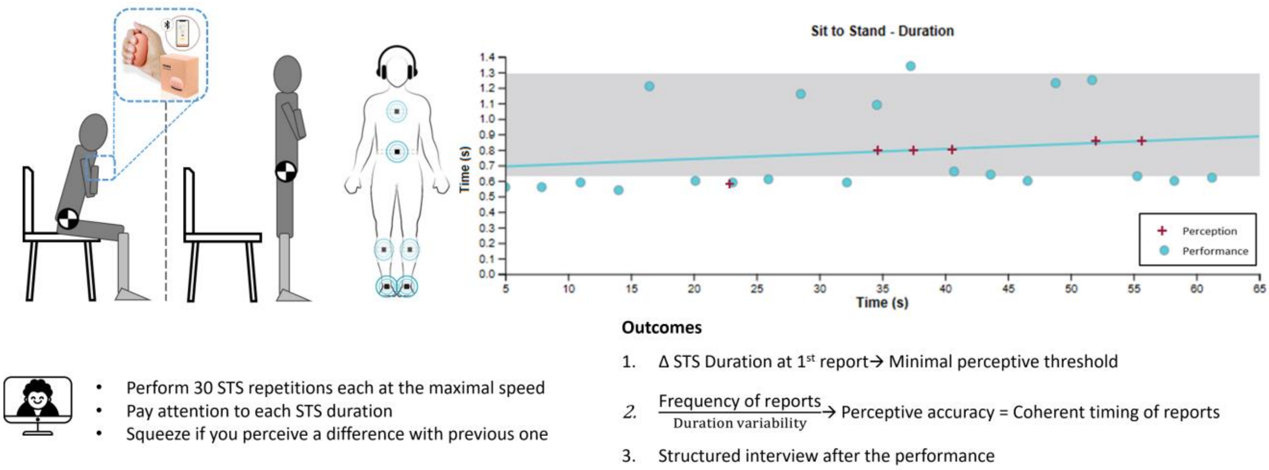


Figure 8 Perceptive accuracy for STS duration variations during repeated STS postural transitions: Task 2 illustration, wearables placement and Perception vs Performance plot graphic illustration.

Repetition of Task 1 and Task 2 with adapted instructions to quantify perceptive accuracy for the detection of changes in movement quality

The participants will repeat the 2 experimental tasks in the same order, but will be asked to detect changes in their movement quality. The different neutral instructions, modified accordingly to the selected objective parameter of movement quality, will be provided to the subject before starting the 6MWT or the STS repetitions.

In this study the movement quality parameter we will focus on will be the 'smoothness' of movements: it will be quantified, with the same wearable sensors configuration as in the previous part, by parameters such as the Harmonic Ratio of gait during Task 1 and the Dynamic Complexity of the STS transition in Task 2, and explained to the participants as 'a movement that happens in a continual fashion, without any interruptions'.

- Task 1 (6MWT overground) instructions: "When you hear the beep tone, squeeze the sensor and start walking at the maximal speed that you can maintain safely for the 6 minutes-length of the experiment. During this period, but only for the straight parts of the walking track, please pay attention to your walking smoothness. Natural variations in your walking smoothness may occur during the test. We want you to notice and report them using the handheld sensor being them positive or negative: this information does not matter for our test and therefore you will not have to indicate it: as soon as you perceive a change in your walking smoothness, squeeze the sensor in your hand to save your report. Report only changes in smoothness that you perceived during the straight parts of the walking tract, all the variations that are due to the turning will be cut out from the analysis. If you will squeeze during a turn, that report will be saved as if it was given three steps before the turn."

- Task 2 (STS) instructions: "When you hear the beep tone, squeeze the sensor and start performing STS repetitions, doing each of them standing up at the maximal speed that you can use to stand up safely. Be aware that we are not asking you to perform as many repetitions you can in a limited amount of time, but that you will be asked to stand up from the chair once every 10 seconds, you just have to do each of the STS at your maximal speed: going from sitting to standing as fast as you can. Natural variations in your STS smoothness may occur between STS repetitions. We want you to notice and, starting from the second repetition, report them using the handheld sensor: if you perceived a change in the smoothness of your stand up movement, being it positive or negative does not matter (you will not have to indicate it), squeeze the sensor in your hand during the resting phase. In between repetitions you will have 10 seconds to decide if to report a change; in the case you didn't notice any change, simply don't squeeze."

This will allow us to explore domain specific differences in perceptive accuracy within subjects.

Research questions for Part A – 'Perception of self-paced performance variations'

- Do PwMS with and without reported fatigue, and HC differ in their perceptive accuracy for detecting walking speed variations and STS duration variations during self-paced experimental protocols? Are these difference modulated by the accumulation of fatigue during the course of the protocol?

- Do PwMS with and without reported fatigue, and HC differ in their perceptive accuracy for detecting gait smoothness and STS smoothness variations during self-paced experimental protocols? Are these difference modulated by the accumulation of fatigue during the course of the protocol?

- Do PwMS and HC differ in the correspondence between measured and subjective (i.e. confidence rating) dimensions of perceptive accuracy?

Hypothesis

- PwMS and HC will differ in the measured outcomes of perceptive accuracy for self-paced walking speed and STS duration variations, lower accuracy is expected in PwMS with higher reported fatigue
- PwMS and HC will differ in the measured outcomes of perceptive accuracy for self-paced gait and STS smoothness variations, lower accuracy is expected in PwMS with higher reported fatigue
- Lower correspondence between measured and subjective (i.e. confidence rating) dimensions of perceptive accuracy is expected in PwMS

Experimental design Part B: 'Perception of imposed performance variations'

Task 1: Perceptive accuracy for imposed speed variations during treadmill walking

On the third day the participants will be tested on the treadmill starting from a familiarization with the range of treadmill speed, personalized accordingly to a subjective and an objective criteria (see above, 'Range of experimentally-induced performance variations – Treadmill walking'). Consequently, the treadmill speed will be quickly returned to comfortable.

Neutral instructions will be provided to the subject before starting the treadmill test by reading the following script: "Start walking when the treadmill moves and try to pay attention to the belt speed, starting at your comfortable level. You should try to maintain your position on the treadmill for the full length of the experiment. Use the lateral bars for hand support in case of brief necessity but release them as soon as you can. We want you to notice, evaluate and report the actual treadmill speed to the experimenter relative to the visual scale on the screen: its starting position on the zero value of the scale represent your comfortable walking speed. Variations in belt speed may occur at any point throughout the experiment, always within you personalized range of speed. Sometimes it is possible that you will not feel any belt speed variation at all. Every 10 seconds you will be asked to communicate the speed level you are perceiving at that point in time, and your report will be recorded".

During the experimental perceptive task the imposed speed will vary from the baseline in an upward/downward fashion with fixed increments (of 0,028m/s) but with randomized time in between every acceleration: the increase in speed will continue for 15 consecutive incremental steps, although never trespassing the participant's maximal speed (derived from their overground performance in first minute of 6MWT, see above), it will stabilize on that value before decreasing toward the baseline speed (with the same number of consecutive steps). As demonstrated in the example, in figure 5, this protocol will last 6 minutes and will impose the absolute magnitude of speed changes (0,42 m/s) for all participants and it will be divided in 3 phases: 1 minute of stable comfortable speed, 150 seconds of speed increments and 150 seconds of speed decrements. The randomization procedure for the time in between every speed variation will ensure that each speed level lasts between 5 and 15 seconds. Each verbal report given by the participants will be immediately recorded by the experimenter.

Obtaining a continuous report of the perceived treadmill speed and confronting it with the actual one will allow us to calculate an intra-subject correlation coefficient between perceived and actual speed, reflecting perceptive correspondence accuracy. This degree of correspondence may vary within a performance and therefore the minute by minute or protocol subphases accuracy dynamics will be also studied (see ‘Data and statistical analysis’).

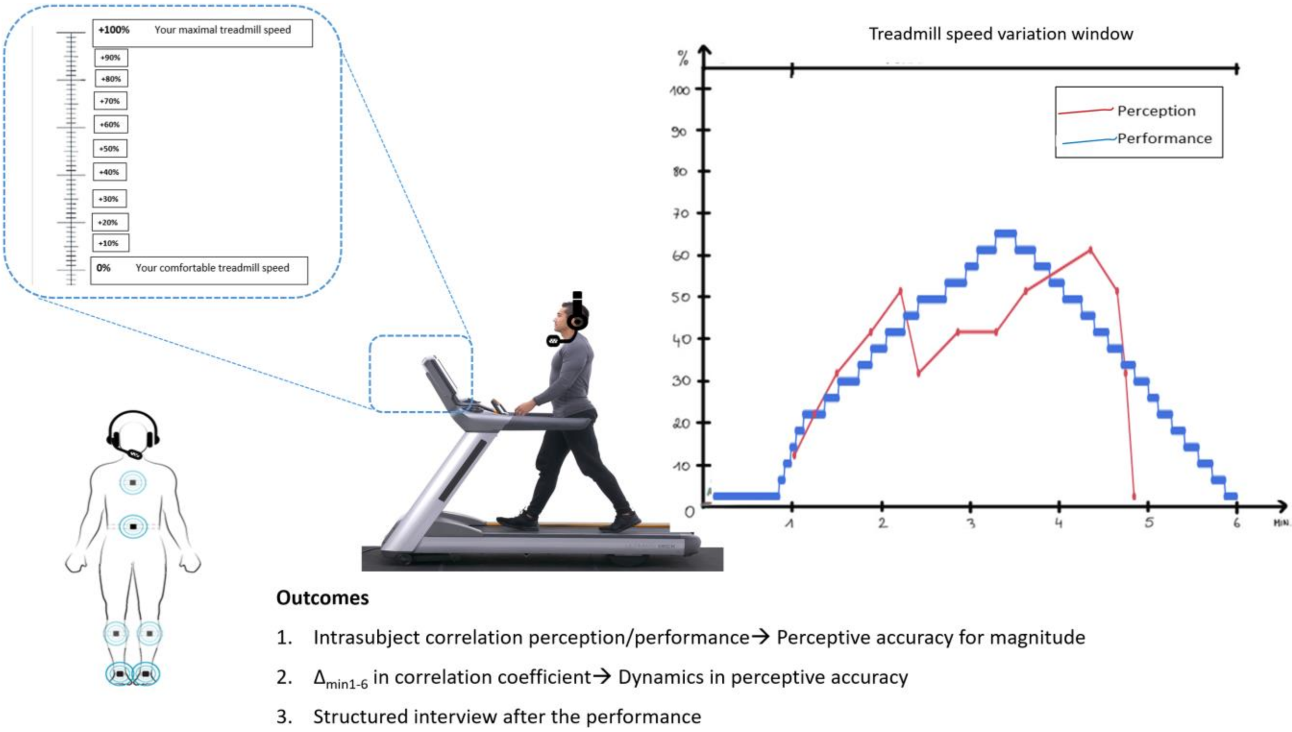


Figure 9 Perceptive accuracy for imposed speed variations during treadmill walking: Task 1 illustration, wearables placement and Perception vs Performance plot graphic illustration (example patter of imposed speed). Δ_{min1-6} indicates that within-protocol variability in the intrasubject correlation will be studied for the different subphases of the protocol.

The intensity of perceived fatigue will be asked just before and immediately after the test using the VAS-F (see Figure 5). Furthermore, a short structured interview will follow including the following question: “On a scale from 0 to 100, how certain are you that you have been precise/accurate in detecting ongoing variations in your performance? Please mark your confidence level on the presented visual scale” (see Figure 7). This question is then followed by an open-ended question where the participant is asked to report on which sensory information he/she was relying to gauge performance variations and give the reports: “On which aspects of your motor performance where you paying attention to detect variations and decide to give a report during the task? Please list them here”.

Task 2: Perceptive accuracy for imposed seat height variations during STS postural transitions

The participants will be tested on a motorized height-adaptable armless chair will allows us to test the perception of imposed sit-to-stand variations in a similar fashion to the treadmill protocol in Part B – Task 1.

A familiarization with the range of seat height, personalized accordingly to the length of the lower leg (see above, ‘Range of experimentally-induced performance variations – Sit to stand), will precede the start of the perceptive task.

Neutral instructions will be provided to the subject before starting the test, by reading the following script: “Start performing STS repetitions at the pace at which you are instructed by the examinator and try, to pay attention, each time, to the seat height. We want you to notice, evaluate and report the seat height to the experimenter relative to the visual scale on the screen: its starting position on the zero value represent your comfortable seat height, the maximum seat height from which I will ask you to stand up. The value of -100, instead, represents the most difficult sit-to-stand you may be asked to perform in the session: the lowest seat-height. Variations may occur at any point throughout the experiment, always within you personalized range. Sometimes it is possible that you will not feel any seat height variation at all. After every STS you will communicate the seat height level you perceived at that point in time, and your report will be recorded”.

The seat will be positioned behind the subject at the baseline normalized seat-height (100% lower leg length). Before the start of the experimental perceptive task the participants will be ensured that the chair will always stay safely positioned behind them and that a person is also standing behind in an attentive state to ensure safety.

During the experimental perceptive task the participant will be guided to execute sit-to-stand transitions paced by the experimenter: during the stance phase (10 seconds) in between STS repetitions, the seat height will be modified starting from the baseline (comfortable seat-height= 120% lower leg length) with fixed decrements (of 5% lower leg length) but with randomized n. of repetitions (0, 1 or 2) in between. The seat-height lowering will continue down to the personalized lowest seat-height, stabilizing on that value before increasing toward the baseline height.

Proceeding, from a personalized baseline, with randomized seat height differences and ensuring blinding of participant in a fashion similar to the above presented treadmill task we will be able to obtain an intra-subject correlation coefficient between perceived and actual seat-height level, reflecting perceptive correspondence accuracy. This degree of correspondence may vary within a performance and therefore the minute by minute or protocol subphases accuracy dynamics will be also studied (see ‘Data and statistical analysis’).

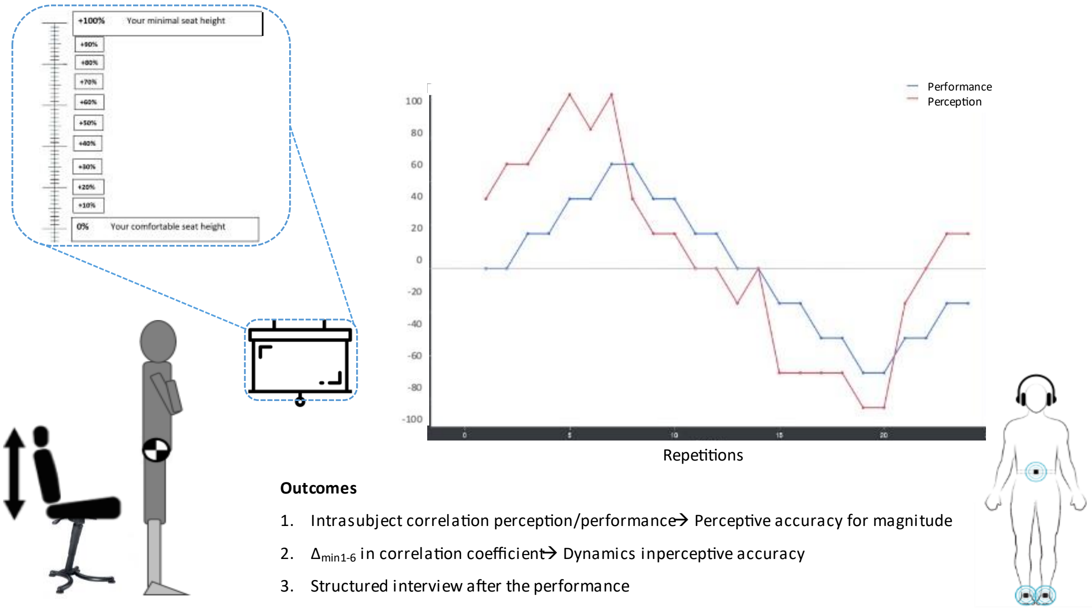


Figure 10 Perceptive accuracy for imposed seat height variations during STS postural transitions: Task 2 illustration, wearables placement and Perception vs Performance plot graphic illustration. $\Delta_{min1\text{-}6}$ indicates that within-protocol variability in the intrasubject correlation will be studied for the different subphases of the protocol.

The intensity of perceived fatigue and a short structured interview will follow in the same way as in task 1 (Treadmill walking).

Research questions for Part B – 'Perception of imposed performance variations'

- Do PwMS with and without reported fatigue, and HC differ in their perceptive accuracy for imposed walking speed variations during treadmill-based experimental protocols? Are these difference modulated by the accumulation of fatigue during the course of the protocol?
- Do PwMS with and without reported fatigue, and HC differ in their perceptive accuracy for imposed STS vertical excursion variations during self-paced experimental protocols? Are these difference modulated by the accumulation of fatigue during the course of the protocol?
- Are these difference modulated by time (different subphases) within the course of the protocol?
- Do PwMS and HC differ in the correspondence between measured and subjective (i.e. confidence rating) dimensions of perceptive accuracy?

Hypothesis

- PwMS and HC will differ in the measured outcomes of perceptive accuracy for imposed walking speed variations during treadmill-based experimental protocols, lower accuracy is expected in PwMS with higher reported fatigue
- PwMS and HC will differ in the measured outcomes of perceptive accuracy for imposed STS vertical excursion variations during self-paced experimental protocols, lower accuracy is expected in PwMS with higher reported fatigue
- PwMS will be less accurate than controls to a larger extend in the last subphase of the protocol (i.e. returning to comfortable speed or seat height levels from the most difficult performance level)
- Lower correspondence between measured and subjective (i.e. confidence rating) dimensions of perceptive accuracy is expected in PwMS

Data and statistical analysis

Motor performance data (gait and STS kinematic, kinetics and spatial-temporal parameters) will be acquired by wearable sensors and extracted from Moveo software (APDM) as .csv file or raw data, and Matlab scripts will be used in case of parameters requiring specific calculation. Data acquired from the participants reports on their perception, during the experimental tasks in Part A and Part B, will be extracted with dedicated Matlab scripts. Statistical analysis will be performed using SPSS (V. 28.01). Tests of normality (Shapiro-Wilk test) will be used to determine if parametric or non-parametric statistical tests have to be used for the comparisons and correlations. The α for all analyses will be set at 0,05.

Clinical assessment outcomes, with a particular focus on the MAIA-2, ISAQ and PAS scores and subscores, will be compared between groups with an independent T test (or with its non-parametric equivalent Mann-Whitney U-Test), to detect significant differences in the subjective beliefs about perceptive abilities.

In the **experimental Part A** we will obtain the participants' minimal perceptive threshold for self-paced performance variations which will be compared between groups with an independent T test (or with its non-parametric equivalent). We will also relate the frequency of the reports with the measured performance variability (coefficient of variation of the selected motor performance parameter: gait speed or STS duration) to obtain a novel outcome measure reflecting perceptive accuracy. We will study it between and within groups using a mixed model ANOVA with time and group as factors to detect significant differences between PwMS and controls and its variations relative to the accumulation of fatigue during the prolonged motor tasks. To investigate its interference with perceptive accuracy the difference between the subjective rate of fatigue (VAS-F) pre-post task protocols will be included in the analysis as covariate.

In the **experimental Part B** within-subject correlations will be calculated between the imposed performance in motor tasks and the perception of its variations. These correlations will be examined separately for different phases of each trial to index perceptive accuracy. Fisher Z transformations (or other types of transformations eg. log transformation) will be applied to these correlations before further analysis, with results back-transformed for reporting. We will study it between and within groups using a mixed model ANOVA with time (protocol subphase) and group as factors to detect significant differences between PwMS and controls and its variations relative to the different subphases of the protocol. To indagate its interference with perceptive accuracy the difference between the subjective rate of fatigue (VAS-F) pre-post protocols will be included in the analysis as covariate. The correspondence between measured and reported dimensions of perceptive accuracy will be calculated as their absolute difference and compared between groups using an independent T test (or with its non-parametric equivalent).

Finally, for the accuracy outcomes derived from both experimental parts we will explore correlations, separated per group, to investigate the relationship between objectively measured perceptive accuracy and factors that potentially interfere with it (demographics, questionnaires and clinical assessments). Then, a regression analysis will be performed to assess the strength of these relationships and identify the most important explanatory factors or predictors.

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