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Home-based Monitor for Gait and Activity Analysis

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Dear JoVe team,

Please find enclosed the manuscript entitled “ActiMyo® - Home-based Monitor for Gait and Activity Analysis " by Charlotte Lilien, Teresa Gidaro, Andreea Seferian, Erwan Gasnier, Marc Grelet, David Vissière, Laurent Servais, that we would like to be evaluated for publication in JOVE.

This work has not been published or submitted elsewhere. All authors have approved the final form of the manuscript. We hope that the manuscript in is a suitable format for filming/publication in Jove and stay at your disposal for any clarification.

Thank you very much,
Charlotte Lilien

TITLE:

Home-Based Monitor for Gait and Activity Analysis

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KEYWORDS:

activity, movement, monitor, outcome, stride, gait, magneto-inertial, wearable sensors

SUMMARY:

This innovative device uses magneto-inertial sensors to permit gait and activity analysis in uncontrolled environments. Currently in the qualification process as an outcome measure in the European Medical Agency, one of the applications will be to serve as a clinical endpoint in clinical trials in neuromuscular diseases.

ABSTRACT:

Current outcomes in neuromuscular disorder clinical trials include motor function scales, timed tests, and strength measures performed by trained clinical evaluators. These measures are slightly subjective and are performed during a visit to a clinic or hospital and constitute therefore a point assessment. Point assessments can be influenced by daily patient condition or factors such as fatigue, motivation, and intercurrent illness. To enable home-based monitoring of gait and activity, a wearable magneto-inertial sensor (WMIS) has been developed. This device is a movement monitor composed of two very light watch-like sensors and a docking station. Each sensor contains a tri-axial accelerometer, gyroscope, magnetometer, and a barometer that record linear acceleration, angular velocity, the magnetic field of the movement in all directions, and barometric altitude, respectively. The sensors can be worn on the wrist, ankle, or wheelchair to record the subject's movements during the day. The docking station enables data uploading and recharging of sensor batteries during the night. Data are analyzed using proprietary algorithms to compute parameters representative of the type and intensity of the performed movement. This WMIS can record a set of digital biomarkers, including cumulative variables, such as total number of meters

walked, and descriptive gait variables, such as the percentage of the most rapid or longest stride that represents the top performance of patient over a predefined period of time.

INTRODUCTION:

A number of potential therapies are in development for treatment of genetic neuromuscular diseases. These diseases include Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) type 3. Subjects with these diseases present initially with proximal lower limb weakness that leads to progressive difficulties in ambulation. The final step in translational research is the demonstration of efficacy of a potential treatment or approach in a clinical trial. Specific, quantifiable, objective, and reliable measures are required. The importance of such measures was recently emphasized by the failure of the phase IIb ataluren trial[1] and the phase III Biomarin trial[2]. One of the likely explanations for these failures was the variability and the nonlinear evolution of the primary outcome measure of these trials, the 6-minute walk test[3] (6 MWT). Increasing reliability and sensitivity to the change of outcome measures and the understanding of the factors leading to their variation could contribute to decrease the number of trial failures related to the main outcome measures.

One of the limitations of the current outcomes is the subjectivity of the assessment. To further increase the objectivity of assessments, Heberer et al.[4] showed that through a marker set and the use of a gait analysis software, there was a significant increase in stride length in patients treated with steroids compared with the naïve group. Hip joint kinetics are early markers of proximal weakness in patients with DMD and are responsive to change with steroid intervention, which is the only available treatment for these patients. Gait laboratories are, however, only available in large clinics. Furthermore, laboratory evaluations are point assessments, and a patient's condition may greatly vary on a day to day basis due to factors such as fatigue, motivation, and intercurrent illness.

The use of continuous and home-based measurement should achieve both a more objective and a more globally representative assessment. In other fields of neurology, for instance Parkinson[5] or multiple sclerosis[6], several studies have assessed the feasibility, reliability, and consistency with other measures of different sensors including accelerometers with or without gyrometers or magnetometers, yet none of these devices is currently a gold standard for evaluation of patients during clinical trials. In the field of neuromuscular diseases, there is currently no validated method for continuous home monitoring of patients. In recent years, through a close collaboration between clinicians and engineers, the Institute of Myology in Paris has developed several devices for upper limb assessment to precisely evaluate upper limb strength and function[7,8,9]. A wearable magneto-inertial sensor (WMIS; i.e., ActiMyo) has been developed in collaboration with a company specialized in navigation systems. Initially a monitoring device dedicated to non-ambulant subjects with neuromuscular disorders such as DMD and SMA[10,11], the same device has now been used to monitor ambulant patients in two different configurations: sensors on both ankles or one sensor at the wrist and the other one at the ankle. The configuration for a non-ambulant population is composed of a sensor at the wheelchair and the other one at the wrist.

This WMIS is able to precisely capture and quantify all movements of the limb on which it is placed. The measuring principle is based on the use of microelectromechanical system (MEMS) inertial sensors and magnetometers operated through magneto-inertial equations.

Dedicated algorithms allow precise qualification and quantification of patients' movements in a non-controlled environment.

The overall goal of the method is to provide identification and quantification of any movement produced by a patient over a pre-defined period of time, and to integrate these measures into disease-specific outcome measures representative of the patient's condition over a period of time.

To effectively assess ambulant and non-ambulant patients with movement disorders at home, the device must be provided to the patient by a trained evaluator who is responsible for making sure that the instructions have been understood. An investigator and a patient manual are provided with the device. This WMIS is currently being used as an exploratory outcome measure in a number of clinical trials for neuromuscular and neurologic diseases (NCT03351270, NCT02780492, NCT01385917, NCT03039686, NCT03368742, NCT02500381). Specific procedures adapted to the pathology and/or to the clinical trial design have been developed.

PROTOCOL:

Any use of the device must be carried out in accordance with the rules established by the reference protocol, validated by the ethics committee and the national regulatory agencies of the country. The use of the device and the various elements attached to it must be done within the intended use described in the patient's manual.

NOTE: To be eligible to use of the WMIS, patient must be over 5 years old, be able to understand and follow the usage rules, provide informed consent, be affiliate or beneficiary of a social security scheme, and be able to comply with all protocol requirements. There are no specific exclusion criteria.

1. Preparing for the participant's visit at the clinical center

1.1. Check the suitcase contents: (1) the docking station to plug the sensors during the night for data uploading onto a USB key and recharging of batteries, (2) the power cord divided into two pieces to connect the docking station to a power supply, (3) the Ethernet cable to permit interface with a router, (4) the two sensors to permit daily activity recording, (5) bands for attachment of the sensors depending on the chosen configuration and ambulatory status of the participant (ankle-ankle: two ankle armbands with two stickers to distinguish the wearing side; ankle-wrist: one ankle armband and one bracelet; wrist-wheelchair: one bracelet and one wheelchair pocket), (6) one participant manual and one investigator manual, (7) one task reminder, (8) a screwdriver to enable replacement of the USB key, and (9) two blank USB keys.

NOTE: If an internet connection is available data transfer occurs automatically

1.2. Print and prepare the assignment form to record the assignment of a device to a participant. This will enable data reconciliation with the subject ID.

2. Training of the subject during the first visit

2.1. Positioning of this WMIS

2.1.1. Based on the data that the researchers are seeking as well as the patient's ambulatory status, use different configurations for the placement of the sensors.

2.1.1.1. For ambulant patients, fix the two sensors either on a wrist and an ankle for upper and lower limb activity recording or on both ankles for only lower limbs activity.

2.1.1.2. For non-ambulant patients, fix one sensor on the wrist and the other one on the wheelchair.

2.2. Explain positioning of the sensors to the participant.

2.2.1. For ambulant participants, fix the two sensors either on a wrist and an ankle or on both ankles.

2.2.1.1. For the wrist-ankle configuration, place one sensor on the wrist of the dominant hand using the provided bracelet so that the waves are pointing toward the fingers. Place the second sensor on the ankle, on the same side as the wrist sensor, above the external malleolus with the waves pointing in the forward direction.

NOTE: The sensor must be placed on top of the wrist.

2.2.1.2. For the ankle-ankle configuration, place a sensor on each ankle, above the external malleolus with the waves pointing in the forward direction.

NOTE: Stickers should be placed on the sensors to indicate the wearing side.

2.2.2. For non-ambulant participants, fix one sensor on the wrist and the other one on the wheelchair.

2.2.2.1. For the wrist-wheelchair configuration, place one sensor on the wrist of the participant's dominant hand using the provided bracelet so that the waves are pointing toward the fingers. Place the second sensor in the bag provided. Attach it on a safe place to the wheelchair.

NOTE: Independently of the used configuration, do not switch sensors around. The sensors should fit snuggly, but not too tightly to the wrist and/or ankle to prevent them from spinning around.

2.3. Explain daily routine for sensors' use to the participant.

2.3.1. Evening routine

2.3.1.1. Plug the docking station into the power supply. Attach the docking station to the router if an internet connection is available. Insert the sensors into the docking station.

2.3.1.2. Localize the two light-emitting diodes (LEDs) on the docking station which indicate the status of the sensors. Once plugged into a power source, be sure the station beeps and the diodes become orange to indicate that the sensor batteries are charging, and that data is being downloaded from the sensors to the USB drive.

NOTE: If the LEDS are still blinking after 5 min, restart the procedure from beginning. If the issue persists, contact the clinical site team.

2.3.2. Morning routine

2.3.2.1. Verify that the LEDs are green, indicating that the sensors batteries are fully charged, and that data has been cleared from the sensors' memory. Remove the sensors from the docking station. Wear the sensors in the configuration demonstrated by the evaluator.

NOTE: If LED on one or both sensors is orange after two consecutive days, contact the clinical center.

2.3.3. Daytime routine

2.3.3.1. Wear the sensors the entire day and place the sensors back on the docking station at the end of the day.

NOTE: Remove the sensors during activities involving water, special medical examinations (e.g., magnetic resonance imaging [MRI], CT-scan, X-ray) or any activity that could damage them, and keep them in a safe place on a firm surface. Resume wearing the sensors after the activity.

2.3.4. At the end of the recording period, tidy up all the device items in the suitcase and bring back the device to the clinical center.

NOTE: Encourage the participant to engage in normal daily activities wearing as much as possible the sensors.

2.4. Complete a dedicated assignment form.

3. Data collection and analysis

3.1. Data collection

NOTE: The sensors record signals continuously for up to 16 h and store the information in an internal memory (**Movie 1**). The docking station enables the downloading of data stored in the sensors at the end of each day and charging of the batteries during the night. Data downloaded to the docking station is stored on a USB drive that can only be accessed by the evaluators.

3.1.1. A standard 64 GB USB drive can hold up to 3 months of daily recording information (approximately 16 h/day). Provide higher or lower capacity USB drives to adjust as closely as

possible to the constraints of the protocols.

3.1.2. If the docking station is not connected to internet, have the evaluator remove the USB drive from the docking station (with the specific screwdriver contained in the suitcase) and replace it with a blank one at the end of the recording period. The USB drive should be sent to the support team for analysis.

NOTE: If the docking station is connected to the internet, data are uploaded to cloud storage. Thus, there is no need to change the USB drive, as all data are automatically deleted from the USB drive once the files are uploaded into the cloud.

3.2. Data analysis

3.2.1. At selected time points during the study, extract data from the cloud storage and analyze data using a dedicated algorithm. Adjust the analysis periods and the monitoring reports based on the clinical study.

REPRESENTATIVE RESULTS:

Data presented here were acquired during clinical trials approved by the ethics committee and the French Regulatory Agency. All patient representatives signed an informed consent.

This WMIS was first used in a clinical study setting in 2012 for controlled and home-based monitoring of upper-limb movements in non-ambulant DMD patients (NCT01611597), which demonstrated the autonomy and feasibility of device use[10]. Variables, such as norm of angular velocity, the ratio of the vertical component of the acceleration to the overall acceleration, the elevation rate, and the computed power, were identified to clinically characterize the upper limb activity of patients in a controlled environment (**Table 1**). In a second step, these variables were correlated with the efficacy of patients during a standardized and validated task, which also allowed testing of device reliability[10]. A more complete validation of variables relevant to non-ambulatory subjects is ongoing.

The validation process in ambulant patients is much more advanced. Recently, the committee for medicinal products for human use (CHMP) wrapped up the public consultation for the qualification of the 95th centile stride velocity (95CSV) as a validated secondary outcome in ambulant DMD patients and the final adoption of qualification opinion is pending. This WMIS allows the identification and measure (height, length, velocity) of each single stride (**Figure 1**) over a long period of time and enables analysis of the distribution of all captured strides, which allows calculation of centile of stride speed and length. The 95CSV appeared to be the most sensitive variable to changes in ambulant DMD patients. The 95CSV provides a sensitive outcome measure that allows a small number of patients per group in a controlled trial. Several other parameters measureable by this WMIS are less sensitive to change than 95CSV but are more closely related to quality of life such as distance walked per hour and the number of falls per hour (**Table 1**).

The precision of the gait trajectory was tested initially in controls, using an optokinetic system that confirmed excellent agreement between trajectories measured by optokinetic system and magnetoinertial sensor[12]. In patients, we assessed the agreement between the distances

measured by this WMIS during a 6 MWT to the distance measured by physiotherapists. **Figure 2** illustrates the ankle trajectory and orientation reconstructed from our WMIS measurements during one lap of a 6 MWT. For this study, data were obtained from 23 ambulant DMD patients (NCT02780492) during 31 6 MWT (some patients performed a second test 6 months later). Results are displayed in **Figure 3**. The difference between the distance measured by our WMIS and the reference 6 MWT (after correction for the length of the turn around the cones, see **Figure 2**) was within 5%.

FIGURE AND TABLE LEGENDS:

Figure 1: Representation of the stride length by the black line which is the computed trajectory of the ankle position during walk reconstructed by this WMIS.

Figure 2: Representation of the trajectory during one lap of a 6 MWT reconstructed by this WMIS.

Figure 3: The 6 MWT distance calculated using this WMIS (y axis) versus the distance measured by the physiotherapist during the same test (x axis) for 31 6 MWT performed by 23 patients.

Movie 1: Reconstruction of the ankle trajectory during walking by using this WMIS.

Table 1: List of parameters.

DISCUSSION:

In the past decade, a number of different systems have been developed, such as an activity monitor (**Table of Materials** [IV]), which uses accelerometric sensors to monitor activities of daily life for energy expenditure quantification[13]. A triaxial accelerometer (**Table of Materials** [V]) was used by Tanaka et al.[14] to monitor activity of preschool children. Lau et al.[15] showed through the combination of a dual-accelerometer (**Table of Materials** [VI]) and a gyroscope (**Table of Materials** [VII]) that gait spatiotemporal characteristics can be precisely determined by the use of inertial sensors. Zijlstra et al.[16] analyzed trunk and 289 compensatory movements of the pelvis occurred during gait using a body-fixed sensor. Most devices used for gait analyses are three-axis accelerometers[17,18,19] (**Table of Materials** [VIII, IX, X]). In addition to accelerometers, our WMIS includes three gyroscopes, a magnetometer, and a barometer. Inertial sensors constitute an interesting technology for evaluation of the motricity of neuromuscular patients due to the difficulty of assessing their reduced movements and their abnormal gaits. Our WMIS can be used to evaluate even the most severely impaired patients, and unlike scales and other tools, provides objective and reliable data. Indeed, the precise measure of strides cannot be achieved with simple wrist worn inertial sensors but requires highly stable and precisely calibrated inertial sensors sampled at a high frequency and placed on the lower limb in order to compute stride trajectory. The same is true of other exploratory outcomes, in ambulant patients, like stair climbing or falls.

We demonstrated that precise estimate of foot trajectory in ambulant DMD is feasible by using our WMIS, which can be worn during daily life. The validated 6 MWT[3] and the North Star Ambulatory Assessment (NSAA)[20] have been correlated with our device's variables describing

spontaneous walk during two weeks recording and are sensitive to change in the DMD population over a 6 month period.

Upper limb activity discrimination during the use of the wheelchair can be challenging. Accelerometry permits the monitoring of physical activity either directly related to wheelchair[21] or upper limb movements during wheelchair movements[22] (**Table of Materials** [XI]). By placing a sensor on the wheelchair and using data from the three-axial accelerometer, gyroscope, and barometer, our WMIS can distinguish upper limb activity from wheelchair and caregiver movements and precisely quantify even very weak movements.

The small size of our sensors is in line with recommendations by Ciuti et al.[23] who noted that the miniaturization of sensors allows new applications in various fields. Improvements in technology now permit easy use, access and promote home-based monitoring of patients through data transmission systems integrated into smart devices, such as smartphones[24,25,26]. However, sensors in smartphones are not calibrated to be used as a clinical outcome measure, and the variability over time is not controlled. Thus, smartphones or tablets can be used for patient-reported outcome measures (**Table of Materials** [XII]) but not as a device to measure movements precisely and continuously.

Several limitations are associated with our device and its protocol. One of the main challenges with continuous home recording is that patient compliance tends to decrease over time. In order to tackle this problem, we had to find the minimal period of time with the lowest variability of the defined variables that can be considered clinically significant for a patient. This was defined as 180 hours of recording, which corresponds to two weeks[27].

A critical step of the protocol is the training. The patient must be trained to use the device, and it is crucial that the evaluator providing the device and the training has first been trained adequately. The best way to optimize the training of the clinical team and the patients to ensure consistent use of the device is by face-to-face training.

Our WMIS will find applications outside the neuromuscular field, for example in evaluation of patients with multiple sclerosis or Parkinson disease, in which other less sensitive and reliable devices have already been tested[28,29]. Qualification processes taking into account measure reliability, variability, confounding factors, minimally meaningful differences, and sensitivity to change must be performed for these subjects as they have been carried out in ambulant patients with DMD described here.

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DISCLOSURES:
Charlotte Lilien, Teresa Gidaro, Andreea Seferian, and Erwan Gasnier are employees at the Institute of Myology and have no affiliation with Sysnav. Laurent Servais is an employee at the Institute of Myology and at the CHRMN Liège and has no affiliation with Sysnav. Marc Grelet is employee of Sysnav. David Vissière is a founder of Sysnav.

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Figure 1

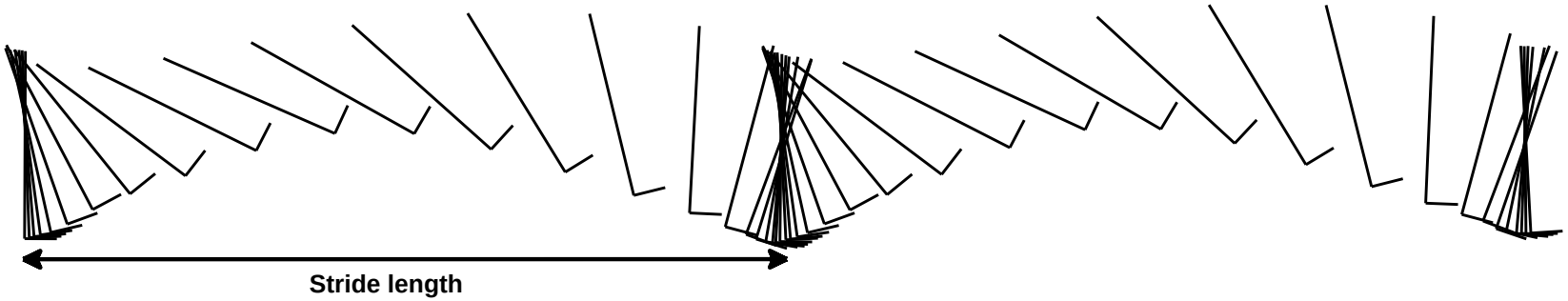

Figure 2

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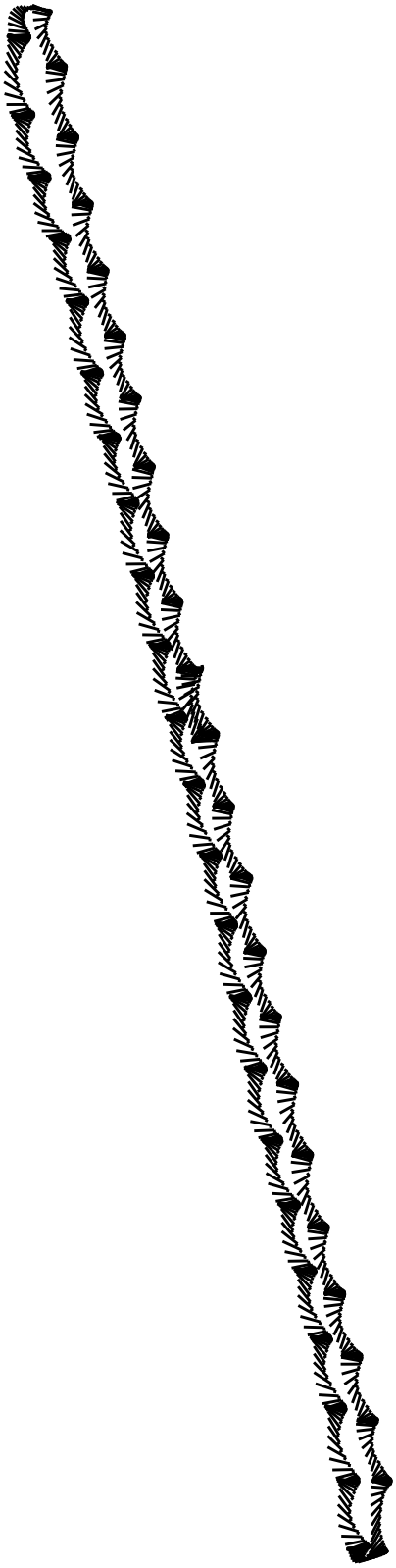

Figure 3

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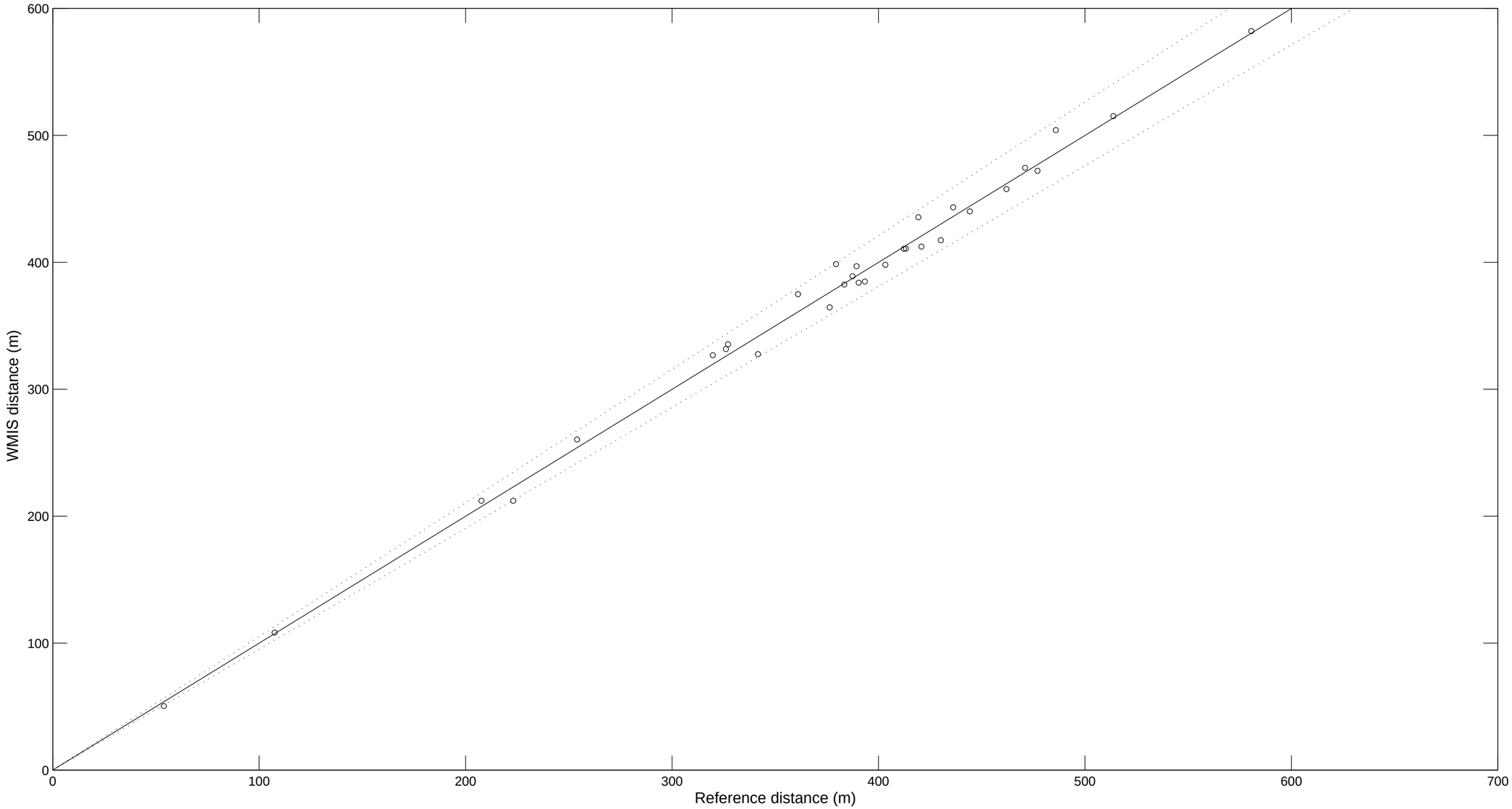
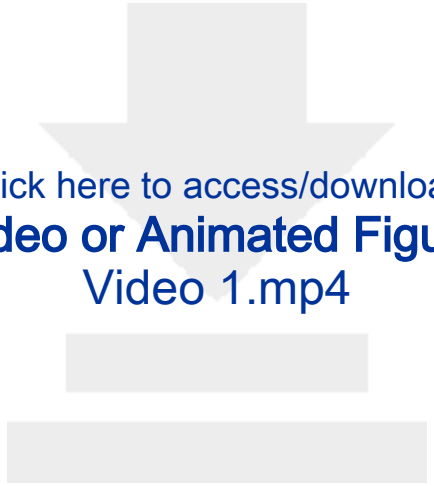


Video or Animated Figure



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Video or Animated Figure

Video 1.mp4

Walking parameters	Upper limb parameters
Percentage of time spent walking (%)	Percentage of time involving upper limb activity (%)
Walked distance per hour (m/h)	Median angular velocity of the wrist (°/s)
Median stride speed (m/s)	95th angular velocity of the wrist (°/s)
95CSV (m/s)	Median vertical acceleration (g)
Median stride length (m)	95th vertical acceleration (g)
95th percentile of the stride length (m)	Median power (W/kg)
Number of falls per hour (count/h)	95th power (W/kg)

Table of Materials

Click here to access/download;Table of Materials;59668_Table of Materials.xls

Refernce number	Name of Material/ Equipment	Company	Catalog Number	Comments/Description
I	ActiMyo Sensors	Sysnav	SF-000080	Wearable magneto-inertal sensors attached to the patient for movment recording
II	Helen Hayes marker set	Vicon	NA	Whole body jumpsuit with predefined Vicon's spots
III	OrthoTrak (Motion Analysis, Santa Rosa, CA, USA)	Motion Lab Systems		Gait analysis software
IV	ActiGraph	ActiGraph Corp	GTM1	Activity monitor, used by researchers to capture and record continuous, high resolution physical activity and sleep/wake information
V	ActivTracer GMS LTD	GMS Co. Ltd Japan	AC-301A	Triaxial accelerometer
VI	ADXL202E dual-accelerometer	Analog Devices	ADXL212AEZ	High precision, low power, complete dual axis accelerometer with signal conditioned, duty cycle modulated outputs, all on a single monolithic IC.
VII	ENC-03J gyroscope	Murata Electronics	ENC-03J	Vibration Sensors
VIII	DynaPort MiniMod	MCROBERTS		Small and light case containing a tri-axial accelerometer, a rechargeable battery, an USB connection, and raw data storage on a MicroSD card
IX	MM-2860 Sunhayato	Sunhayato	MM-2860	3-axis accelerometer
X	MicroStone MA3-10Ac	MA3-04AC	Microstone Co.	Acceleration sensors
XI	RT3 Activity monitor	Abledata	NA	Triaxial accelerometer
XII	Aparito	aparito	NA	Wearables and disease specific mobile apps to deliver patient monitoring outside of the hospital; Elin Davies, Aparito: https://www.aparito.com/
	Docking station	Sysnav	SF-000118	
	Sensor	Sysnav	SF-000080	
	Bracelet (black/grey L) (black/grey S) (black/yellow L) (black/yellow S)	Sysnav	ZZ-000093 ZZ-000094 ZZ-000247 ZZ-000248	
	Patient manual	Sysnav	FD-000086	
	Ethernet cable (2 m max.)	Sysnav	IC-000458	
	Power cable (EU) (UK) (US)	Sysnav	ZE-000440 ZE-000441 ZE-000442	
	Power supply unit	Sysnav	ZE-000443	
	Ankle strap	Sysnav	ZZ-000462	
	Small bag	Sysnav	ZZ-000033	

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Title of Article: ActiMyo - Home - based Monitor for Gait and Activity Analysis

Author(s): Charlotte LILIEN, Teresa GIDARO, Andreea SEFERIAN, Erwan GASNIER, Marc GRELET, DAVID VISSIERE, Laurent SERVAIS

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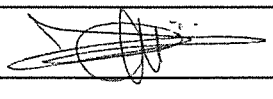
Signature:	
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Dear Dr. Lilien,

Your manuscript, JoVE59668 "ActiMyo® - Home-based Monitor for Gait and Activity Analysis," has been editorially and peer reviewed, and the following comments need to be addressed. Note that editorial comments address both requirements for video production and formatting of the article for publication. Please track the changes within the manuscript to identify all of the edits.

Please note that the manuscript has been modified to include line numbers and minor formatting changes. The updated manuscript is attached and please use this updated version for future revisions.

After revising and uploading your submission, please also upload a separate rebuttal document that addresses each of the editorial and peer review comments individually.

Please submit each figure as a vector image file to ensure high resolution throughout production: (.svg, .eps, .ai). If submitting as a .tif or .psd, please ensure that the image is 1920 x 1080 pixels or 300 dpi.

Your revision is due by **Feb 25, 2019**.

To submit a revision, go to the JoVE submission site and log in as an author. You will find your submission under the heading "Submission Needing Revision".

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1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues. The JoVE editor will not copy-edit your manuscript and any errors in the submitted revision may be present in the published version.

We changed this.

2. Title: Please remove commercial language (ActiMyo®).

We changed this.

3. Keywords: Please provide at least 6 keywords or phrases.

We changed this.

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We changed this.

6. Please rephrase the Introduction to include a clear statement of the overall goal of this method.

We changed this.

7. Please include an ethics statement before the numbered protocol steps, indicating that the protocol follows the guidelines of your institution's human research ethics committee.

We changed this.

8. Protocol: Please refrain from using indentations.

We changed this.

9. Please revise the protocol to contain only action items that direct the reader to do something (e.g., "Do this," "Ensure that," etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as "could be," "should be," and "would be" throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a "Note." Please include all safety procedures and use of hoods, etc. However, notes should be used sparingly and actions should be described in the imperative tense wherever possible. Please move the discussion about the protocol to the Discussion.

We changed this.

10. Everything in the protocol (except for the introductory ethics statement) should be in a

numbered step (in the imperative tense and with no more than 4 sentences), numbered header, or a 'Note'. Please move the introductory paragraphs of the protocol to the Introduction, Results, or Discussion (as appropriate) or break into steps.

We changed this.

11. The Protocol should be made up almost entirely of discrete steps without large paragraphs of text between sections. Please simplify the Protocol so that individual steps contain only 2-3 actions per step and a maximum of 4 sentences per step. Use sub-steps as necessary. Please move the discussion about the protocol to the Discussion.

We changed this.

12. 2.1: Please describe the inclusion and exclusion criteria of participating patients.

We changed this.

13. Please remove the embedded figures/table from the manuscript.

We changed this.

14. Please include all the Figure Legends together at the end of the Representative Results in the manuscript text.

We changed this.

15. Please upload Table 1 to your Editorial Manager account as an .xls or .xlsx file.

We changed this.

16. For in-text references, the corresponding reference numbers should appear as superscripts after the appropriate statement(s) in the text (before punctuation but after closed parenthesis). The references should be numbered in order of appearance.

We changed this.

17. Please ensure that the references appear as the following: [Lastname, F.I., LastName, F.I., LastName, F.I. Article Title. Source. Volume (Issue), FirstPage – LastPage (YEAR).] For more than 6 authors, list only the first author then et al. Please do not abbreviate journal titles. See the example below:
Bedford, C.D., Harris, R.N., Howd, R.A., Goff, D.A., Koolpe, G.A. Quaternary salts of 2-[(hydroxyimino)methyl]imidazole. Journal of Medicinal Chemistry. 32 (2), 493-503 (1998).

We changed this.

Reviewers' comments:

Reviewer #1:
This manuscript entitled "ActiMyo® - Home-based Monitor for Gait and Activity Analysis" aimed to enable home-based monitoring of gait and activity for patients with neuromuscular diseases through record a set of digital biomarkers. But there are several questions should be addressed before this manuscript can be accepted for publication, which list below. I give a major revision for this manuscript.

Specific comments:
1. In Introduction part (Line 68-71), to make the complete structure of the sentence, please change the sentence to "In a 69 controlled environment, Heberer et al. (4) showed that through the Helen Hayes marker set and use of the OrthoTrak (Motion Analysis, Santa Rosa, CA, USA), there was a significant 71 increase in stride length in patients treated with steroids compared with the naïve group."

We changed this.

2. In the part of "Representative Results" (Line 277), please increase the clarity of the Figure

We have increased the clarity of the legend : *6 MWT d*istance calculated using ActiMyo® *(Y axis)* versus the distance measured by the physiotherapist *during the same test (X axis)* for 31 6 MWT performed by 23 patients.

4. In the part of "Discussion" (Line 288-289), change the sentence to "Zijlstra et al. (13) analyzed trunk and 289 compensatory movements of the pelvis occured during gait using a body-fixed sensor".

We changed this.

5. Please check the Bibliography format in the whole article. For example, change "Zijlstra et al." to "Zijlstra et al. (13)".

We changed this.

6. In the part of "Discussion" (Line 315-318), change the sentence to "Improvements in technology now permit easy use, access and promote home-based monitoring of patients through data transmission systems integrated into smart devices, such as smartphones".

We changed this.

Reviewer #2:
Manuscript Summary:
This manuscript exposes how to use a device with embedded inertial sensors to objectively monitor a patient movement during daily activities.
The manuscript is well written, and I have a few minor comments/suggestions.

Minor Concerns:
Abstract, Lines 51-52: "…top stride speed or stride length…"
Please clarify: it would be an average stride speed peak? Or the highest stride speed/largest stride length?

We have clarified: such as the X% most rapid or longest stride that represent the top performance of patient over a predefined period of time.

Introduction
Line 68: I think this sentence is out of context, and it is not a good introduction to the corresponding paragraph. :

We have improved the transition between the two paragraphs.

Line 91: I think that with only two sensors at the ankles or at the wheelchair/wrist and at one ankle, the device is not able to "precisely" capture "all" movements.
It is just a matter to rewrite the sentence.

We agree with the reviewer and have rephrased accordingly.

Line 94: Idem - "…precise qualification and quantification of patient motor activity …". I think would be better an expression as "…quantification of a patient "general" motor activity…"

We agree with the reviewer and have rephrased accordingly.

Protocol
Item 2.1
It is not clear in what situation I have to use, or would be advisable to use, an ankle-wrist configuration or an ankle-ankle configuration.
I think some comments here would be welcome.

We clarified this in the manuscript.

Item 3.1
Lines 227-228: "…analyst will retrieve data from the cloud storage." Or from USB drives, if the patient does not have an internet connection. Am I right?

The data recovered from the USB drive are manually uploaded to the cloud storage. The USB drive has only a role of back up if no internet connection is available at patient's home. We clarified this in the manuscript.

Representative Results
Line 247: What measurements? Please, be more specific. Maybe it would be more appropriate to use the word "identification".

We have rephrased by identification and measure (height, length, velocity)

Discussion
Line 287: Please, add the word "spatiotemporal" after the word "gait".

We changed this.

Line 293: Please, change the word "necessary" by "interesting" or "one alternative", or similar.

We changed this.

Line 296: Good! I agree.
Line2 298-299: This sentence is out of context, and it is not a good introduction to the corresponding paragraph.

We have deleted it.

A discussion of other potential variables that can be extracted from ActiMyo, different from that showed in Table 1, would be welcome. Otherwise, it is not clear the utility of having triaxial sensors, or gyroscope, magnetometer and barometer. Only accelerometer would be enough for the variables shown in Table 1.

We do not agree at all on this statement. Variables in Table 1 cannot be measured for most of them, and cannot be measured precisely for all of them using accelerometers only. However, we agree that discussion of exploratory variables and the need of magneto inertial technology to measure them would increase the impact of the discussion. We have added this short discussion.

A barometer, for example, would be interesting to detect going up and down stairs or inclines, I suppose. A small paragraph discussing this question would be welcome.

We clarified this.

Figure 1, Line 271: Please, indicate what is the gray line, and how it is computed.

We clarified this.

Figure 2, Line 273: Idem

We clarified this.

Figure 3: Please, increase the font size, and do not use gray color

We changed this.

Reviewer #3:
Manuscript Summary:
Thank you for giving me the opportunity to review this manuscript in which the authors describe the application of inertial sensors-based system to acquire and process information about gait and movement in home setting.
The study is interesting, I have only some concerns that I'm sure the authors will easily address:

1) Accelerometers are widely used since at least two decades to obtain information about spatio-temporal and kinematic parameters of gait, as well as about physical activity, in individuals affected by a range of neurologic disorders. However, reading the paper, it looks like the authors are the first (or among the first) to use them for this purpose. Please, expand the Introduction quoting suitable papers (or reviews) to inform reader of what has been already done in this field, both in laboratory and clinical settings.

We agree with the reviewer and have added this point in the discussion.

2) In order to assess the validity of their measurements in terms of distance traveled by the patients, the authors compared the accelerometric data with 6MWT. While this approach is certainly useful to support the information that their system provide clinically meaningful data, it tells little about the accuracy. Did the authors perform any comparison of the spatio-temporal parameters with a real gold-standard?

We agree with the reviewer and have added the optokinetic validation point in the representative results.
