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ORIGINAL COMMUNICATION

Wearable motion sensors to track tremor changes after radiosurgical thalamotomy

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Dear Sirs,
Stereotactic radiosurgery and magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy have proved highly effective for treating medication-resistant tremor related to Parkinson's disease (PD) or essential tremor (ET), resulting in significantly greater reduction in tremor and improvement in quality of life [4]. Currently, the main anatomical target is the thalamic ventral intermediate nucleus (Vim) involved in the dentate-ponto-cerebello-thalamo-cortical pathway, one of the circuits allegedly implicated in the pathophysiology of tremor generation [9].

Most studies on Vim thalamotomy for tremor reported the evaluation of motor symptoms before and after treatment through disorder-specific clinical scales [4, 5, 11]. Motor symptoms' severity is usually measured using the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in patients with PD, while the Fahn-Tolosa-Marin (FTM) clinical tremor rating scale and The Essential Tremor Rating Assessment Scale (TETRAS) are usually adopted to grade ET [10]. Although widely used in clinical and research practice, these scales present some limitations, such as high inter-rater variability among different clinicians or different medical centers and inter-rater variability over time [14], hence undermining the possibility to compare results.

In this context, the application of smart technologies for movement disorders has increased in recent years. Wearable sensors, in particular, are becoming crucial in supporting clinicians performing early diagnosis, differential diagnosis, and objectively quantifying symptoms over time [14]. Several authors already demonstrated the potential of new technology for PD diagnosis [1] and management [14]. Likewise, this technology has recently been applied to evaluate ten ET patients who underwent deep brain stimulation (DBS) [3]. On the contrary, wearable sensors applications data for quantifying Vim thalamotomy efficacy for tremor are still lacking.

For this purpose, we investigated the application of wearable sensors technology for medication-resistant tremor in a PD patient who underwent Gamma Knife radiosurgery (GKRS) Vim thalamotomy and was followed up for one year. The patient was recruited from our clinic within the framework of an ongoing longitudinal project. Informed consent was obtained from the participant, and the study was approved by the institutional review board.

A 76-year-old right-handed woman with a 13-years history of PD and affected by several medical comorbidities (i.e., high blood pressure, atrial fibrillation requiring anticoagulation drugs) was deemed to be a candidate for Vim thalamotomy for treatment of severe refractory tremor by a joint multidisciplinary consultation. On neurological examination, in addition to resting tremor, she had a bilateral postural and kinetic tremor greater in the left than in the right

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upper limb. Tremor of the head, neck and/or voice was not present. Bradykinesia and rigidity symptoms were well controlled with medications (Levodopa/Benserazide 200/50 mg tid). She was treated with Propranolol and then Primidone for treating tremor, but she was forced to suspend them both after few days due to the presence of medication-related side effects. Brain MRI identified a cerebral vasculopathy, whereas at neuropsychological evaluations, no dementia or major depression was found. Based on these findings, the patient was considered a good candidate for unilateral GKRS thalamotomy targeting the left Vim nucleus with the purpose of improving disabling tremor in the dominant hand (right side).

Stereotactic planning was performed on a preoperatively obtained high-resolution 3 Tesla brain MRI. Before treatment, a stereotactic frame (Leksell Elekta, Stockholm, Sweden) was placed under local anesthesia, after which a computed tomography (CT) scan of the head with localizer was obtained and fused to the preoperatively obtained MRI using Elekta GammaPlan software (Elekta Instruments AB, Stockholm, Sweden). The treatment plan was performed using the Leksell Gamma Knife Icon model: the anterior commissure and posterior commissure were identified; one single shot was placed on the left Vim targeted at 14 mm lateral to the AC-PC line (X coordinate), 25% of the AC–PC distance (plus 2 mm) anterior to the PC (Y coordinate) and 2 mm superior to the AC–PC line (Z coordinate) with a maximal prescription dose (Dmax) of 130 Gy via a 4-mm collimator with sector blocking to reduce the dose delivered to the internal capsule.

The patient was assessed using clinical evaluation and 3 inertial measurement units (Xsens MTw Awinda wearable sensors) with a customized software developed by Khymeia Group (Padua, Italy) before treatment and over the follow-up period (at 3, 6 and 12 months after treatment). At study entry and during follow-up visits, an experienced movement disorder physician performed clinical assessments. The patient was examined in ON state (i.e., the period when the dopaminergic medication works, and symptoms are well controlled). Demographic, clinical and family data were obtained using a semi-structured interview. Levodopa equivalent daily dose (LEDD) was calculated [15]. Disease severity was defined using the Hoehn and Yahr stage score [6]. MDS-UPDRS [10] was applied to evaluate non-motor symptoms (MDS-UPDRS I), motor symptoms (MDS-UPDRS II), motor signs (MDS-UPDRS III), and motor complications (MDS-UPDRS IV).

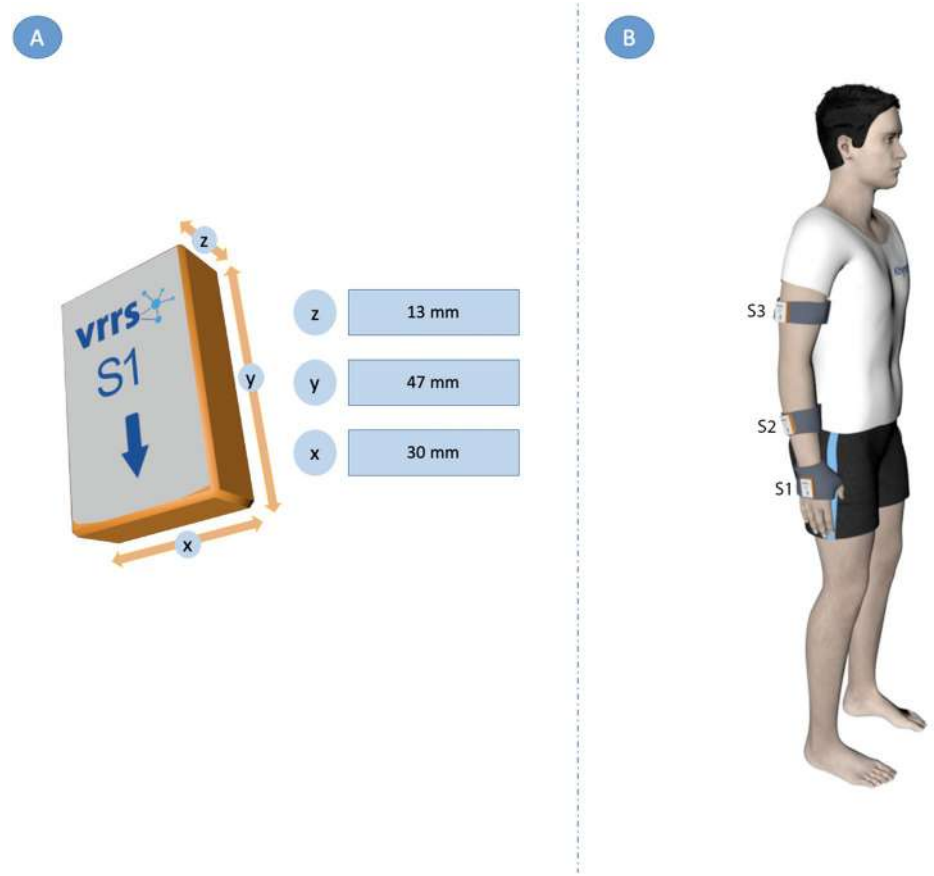

Fig. 1 Wearable device overview and sensors placement. **a** The Xsens MTw Awinda wearable sensor is a miniature inertial measurement unit with a package size of 47 × 30 × 13 mm and a weight of 16 g. **b** Placement of the sensors: the first sensor (S1) was positioned on the dorsum of the hand, the second sensor (S2) on radial diaphysis and the third sensor (S3) on the humeral diaphysis. Considering the Cardan angle system, the movement of the sensor S1 around the Z axis is considered "roll" and corresponds to pronation/supination of the forearm; the movement around Y axis is considered "yaw"; furthermore, subtracting the "yaw" signal from sensor S2, corresponding to elbow flexion/extension and the movement around the X axis is considered "pitch" and corresponds to the wrist flexion/extension. Also, considering S3, the "roll" axis corresponds to humeral internal/external rotation, "yaw" corresponds to humeral flexion/extension and "pitch" corresponds to abduction/adduction

The MTw Awinda is a miniature Inertial Measurement Unit (IMU) with a package size of 47 × 30 × 13 mm and a weight of 16 g (Fig. 1a). It provides highly accurate drift-free 3D orientation data recording tri-axial data from an accelerometer (range: ± 4G) and gyroscope (range: ± 2000°/s; ± 160 m/s2; ± 1.9 Gauss) at a sampling rate of 40 Hz with 30 ms of latency and a synchronization between sensors within 10 µs. Static accuracy "Roll/Pitch" is 0.5 deg RMS while "Heading" is 1 deg RMS. Dynamic Accuracy "Roll/Pitch" is 0.75 deg RMS and "Heading" is 1.5 deg RMS [12]. The participant wore three IMU sensors per arm: the first sensor (S1) was positioned on the dorsum of the hand, the second sensor (S2) on radial diaphysis and the third sensor (S3) on the humeral diaphysis. All sensors were fixed to the skin surface with adhesive dressing and positioned to be aligned between them while standing with arms resting at sides (Fig. 1b). According to a multidisciplinary approach involving neurosurgeons, neurologists, and physiotherapists, five tasks of 15 s' duration each were chosen to assess rest, postural and action tremor severity before treatment and over the follow-up (at 3, 6 and 12 months after treatment). Each task was carried out in three different conditions (standing, sitting on a chair and supine). In detail, *rest tremor* was assessed with the arm resting on the armrests of a chair during the condition "sitting on a chair" (Fig. 2a); with a "supine" patient, resting on a bed with arms supported and with forearms and wrists dangling off the bed (Fig. 2b); during the "standing" condition, the rest tremor was assessed with arm resting at sides (Fig. 2c). *Postural tremor* was assessed with arms raised, keeping the humerus straight parallel to the floor with elbow extended (Fig. 2d). *Action tremor* was evaluated by the task "hip-shoulder", which consisted in repetitive arm movements leading one hand from the ipsilateral hip to the contralateral shoulder (Fig. 2e). The following parameters were extracted from the sensors signal processing at each task: 1. amplitude of tremor (degree of movement); 2. angular velocity of tremor (degree of movement/seconds); 3. mean frequency of tremor (hertz).

The sensors' signals were captured and transferred to a personal computer via a wireless link. They were therefore processed using Matlab (R2015b) for analysis. A tremor signal is defined as a time series obtained from the x-axis of an angular velocity sensor. Since tremor frequencies of PD and ET can overlap with range from 4 to 8 Hz, and to exclude low-frequency high-amplitude signal caused by movements while performing kinetic task, tremor signals were filtered with a 10th-order Butterworth band pass filter with cut-off frequencies of 3 and 10 Hz. To correct for occasional dropped samples and nonuniform sampling rates, data recordings from each task were interpolated to the intended

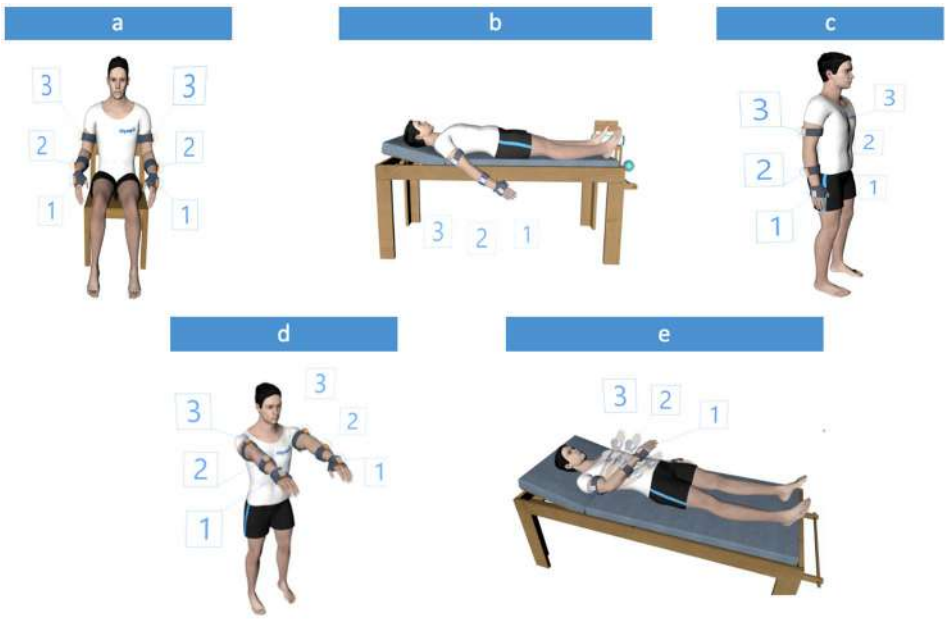

Fig. 2 Scenario of arm movements for tremor assessment using wearable sensors. **a** Rest tremor assessed with the arm resting on the armrests of a chair during the condition "sitting on a chair"; **b** Rest tremor assessed with a "supine" patient, resting on a bed with arms supported and with forearms and wrists dangling off the bed; **c** Rest tremor evaluation during the "standing" condition with arm resting at sides; **d** Postural tremor assessed with arms raised, keeping the humerus straight parallel to the floor with elbow extended. **e** Action tremor in a "supine" patient evaluated by the task "hip-shoulder", which consisted in repetitive arm movements leading one hand from the ipsilateral hip to the contralateral shoulder

Table 1 Patient's baseline and follow-up clinical assessment

Clinical Features	Baseline	3-months	6-months	12-months
Hoehn and Yahr	3	3	3	3
MDS-UPDRS III postural tremor (3.15) right side	3	3	2	2
MDS-UPDRS III postural tremor (3.15) left side	3	3	3	3
MDS-UPDRS III kinetic tremor (3.16) right side	4	2	1	1
MDS-UPDRS III kinetic tremor (3.16) left side	4	3	3	3
MDS-UPDRS III rest tremor (3.17, 3.18) right side	6	5	4	4
MDS-UPDRS III rest tremor (3.17, 3.18) left side	7	7	6	6
MDS-UPDRS III overall tremor right side	13	10	7	7
MDS-UPDRS III overall tremor left side	14	13	12	12

Abbreviations: *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale

sampling rate (40 Hz for Xsens MTw Awinda) using a cubic spline interpolation.

Pre- and post-operative clinical data are summarized in Table 1. During the pre-operative evaluation, the Hoehn and Yahr score was 3; MDS-UPDRS part I was 11, part II 27, part III (ON-medication) 59, and part IV was 5. Treated hand MDS-UPDRS postural tremor (item 15) and kinetic tremor (item 16) scores were 3 and 4, respectively, rest tremor (item 17 plus 18) was 6. MDS-UPDRS motor scores of the upper right limb were lower at 3, 6 and 12 months after thalamotomy compared to the baseline (Table 1).

Referring to the motion sensor measurements, we observed an improvement over time in all analyzed parameters, tremor frequency, amplitude and angular velocity during any condition (rest, postural and action tremor evaluation). Selected motion sensor measurements during tasks at baseline and over the follow-up are presented in Fig. 3. The amplitude of tremor was the most improved measurement. Furthermore, the percentage of tremor improvement between baseline and 12 months after treatment ranged from 21% in rest tremor to 89% in action tremor analysis (52% in postural tremor) in line with MDS-UPDRS part III results (Table 1). Therefore, wearable motion sensors not only objectively confirm the results of clinical scales for tremor evaluation (subject-specific), but also provide specific details on tremor features and their variation over time. Notably, in motion sensor analysis, maximal benefit was not achieved until 6–12 months of follow-up (Fig. 3, Table 1). As expected, the tremor that affected the left side did not change after treatment at motion sensor analysis.

According to our results, wearable sensors may offer several advantages over clinical scales to address tremor. Some studies describing PD patients treated with DBS showed that strong changes in the clinical tremor assessment (using the MDS-UPDRS motor score) between DBS off and on did not always result in strong changes in the tremor parameters analyzed by motion sensors [3, 13]. It must be considered that clinical scales, such as the MDS-UPDRS motor score, include rating from different parts of the body in different movement conditions; hence, it might not be always adequate to measure tremor changes in one single body part [13, 14]. The pre-operative and post-operative evaluation of tremor with sensors not only allows to assess the tremor frequency, the amount of oscillations per second and the variation measured in cycles per second (Hz), but also to evaluate the degree of linear or angular displacement of the upper limb (tremor amplitude, measured in millimeters or degrees) and the angular velocity, therefore providing a more complete representation of human movement.

Regarding the practical application of the devices, our sensors, as stated by Cavallo et al. [2], seem to be optimal in terms of wearability, portability, light weight, performance and ease of use, representing an optimal solution in this field.

Importantly, we were able to quantify tremor frequency, angular velocity, and amplitude over time within four time points. It is well known that the mean time to tremor response after radiosurgery is 4.8 months, with a range from 3 weeks to 12 months [8, 11]. Although in a single patient, our results are in line with the medical literature.

Furthermore, our findings align with clinical experience and may reflect relatively selective effect of Vim thalamotomy interrupting cerebello-thalamic outflow via disruption of dentate-rubro-thalamic tract thereby improving action tremor, whereas PD rest tremor may have greater contribution from basal ganglia outflow pathways not specifically targeted in a Vim thalamotomy.

Unlike radiosurgery, thermocoagulation effects of MRgFUS induce a significant immediate reaction, leading to a direct cessation of tremor during treatment [5, 7]. For this reason, in our experience, wearable sensors' ease of use makes them applicable during MRgFUS intra-procedural lesion mapping. This could be crucial to better detect the thalamic area associated with optimal tremor outcome.

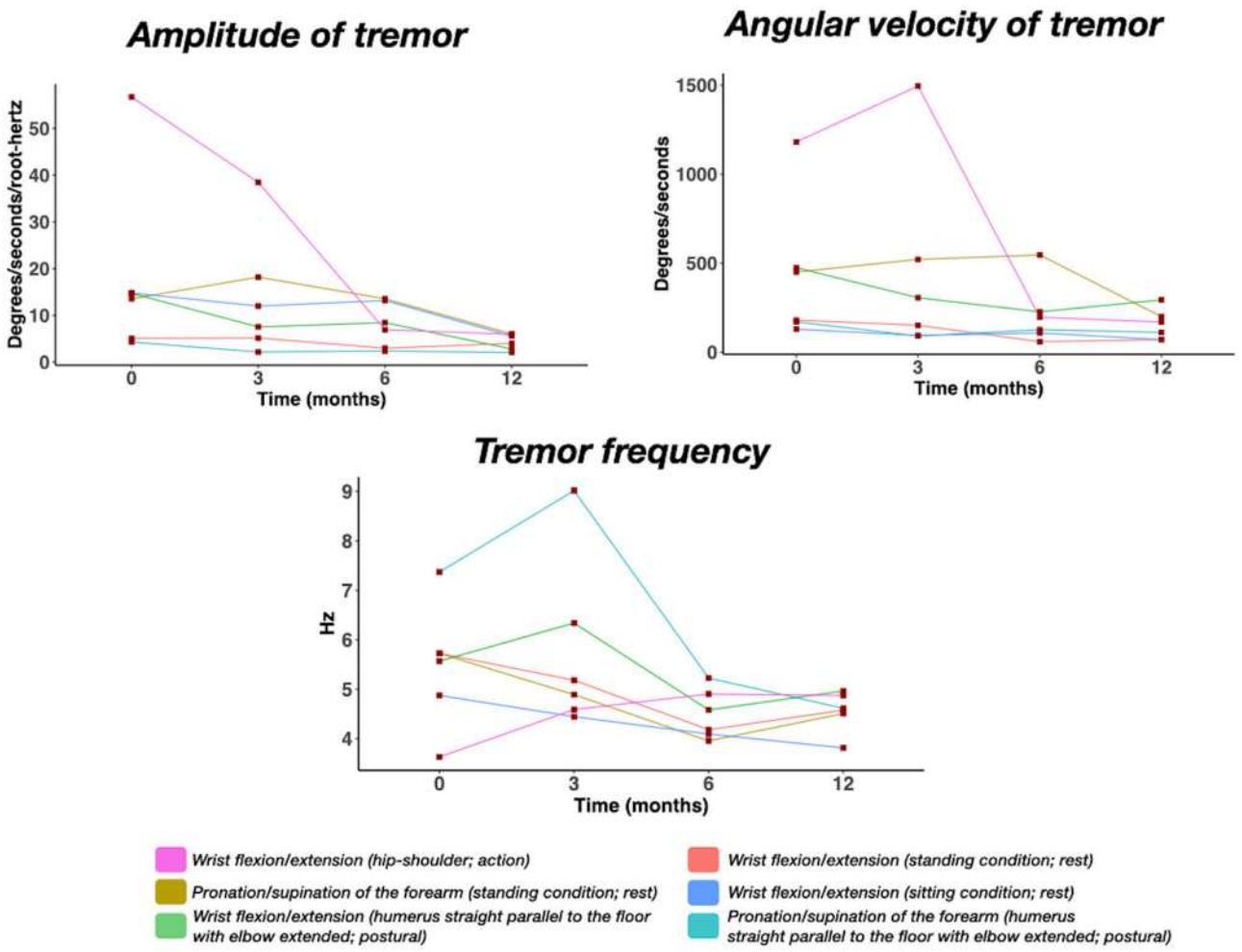

Fig. 3 Individual patient inertial parameters (right arm) according to different tasks before treatment and over time (at 3, 6 and 12 months after treatment): Amplitude of tremor; Angular velocity of tremor; Tremor frequency

There is no study directly comparing the outcomes of MRgFUS versus radiosurgery thalamotomy [7]. Since the primary efficacy outcome is the difference in tremor before and after treatment, the use of wearable sensors may be the objective method to clarify differences in terms of tremor suppression among the two procedures.

In conclusion, wearable sensors were able to objectively quantify tremor after thalamotomy. These new insights may advance our understanding of the progressive tremor changes after radiosurgery and of lesion mapping during MRgFUS. Future research including larger groups of patients observed over longer periods of time are required to replicate these findings.

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Declarations

Conflicts of interest L. Albano was a recipient of the Lars Leksell Fellowship. D. Emedoli, S. Basaia, R. Balestrino, E. Pompeo, L.R. Barzaghi, S. Iannaccone and P. Mortini report no disclosures. F. Agosta is Section Editor of neuroimage: Clinical; has received speaker honoraria from Biogen Idec, Roche and Zambon; and receives or has received research supports from the Italian Ministry of Health, Arisla (Fondazione Italiana di Ricerca per la SLA), Fondation Recherche Alzheimer (France) and the European Research Council. M. Filippi is Editor-in-Chief of the Journal of Neurology, Associate Editor of *Human Brain Mapping*, Associate Editor of *Radiology*, and Associate Editor of *Neurological Sciences*; received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Neopharmed Gentili, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Ethical standard statement Written informed consent in respect of this case report was obtained in accordance with the Declaration of Helsinki. No ethics board approval was required for this case report.

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