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Locomotor coordination in patients with Hereditary Spastic Paraplegia

G. Martino[a,b,*], Y. Ivanenko[b], M. Serrao[c,d], A. Ranavolo[e], F. Draicchio[e], C. Casali[d], F. Lacquaniti[a,b,f]

[a] Centre of Space Bio-medicine, University of Rome Tor Vergata, 00133 Rome, Italy
[b] Laboratory of Neuromotor Physiology, IRCCS Santa Lucia Foundation, 00179 Rome, Italy
[c] Rehabilitation Centre Policlinico Italia, 00162 Rome, Italy
[d] Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, 04100 Latina, Italy
[e] INAIL, Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, Monte Porzio Catone, 00078 Rome, Italy
[f] Department of Systems Medicine, University of Rome Tor Vergata, 00133 Rome, Italy

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ABSTRACT

Locomotion is a complex behaviour that requires the coordination of multiple body segments and muscle groups. Here we investigated how the weakness and spasticity in individuals with Hereditary Spastic Paraplegia (HSP) affect the coordination patterns of the lower limbs. We analysed kinematics and electromyographic (EMG) activity from 12 leg muscles in 21 persons with HSP and 20 control subjects at matched walking speeds. To assess the locomotor coordination, we examined the covariation between thigh, shank and foot elevation angles by means of principal component analysis and the modular organization of EMG patterns using the non-negative matrix factorization algorithm. The characteristic features of the HSP gait consisted in changes of the elevation angles covariation, the shape of the gait loop, reduced range of motion of the distal segments and significantly lower foot lift. The EMG factorization analysis revealed a comparable structure of the motor output between HSP and control groups, but significantly wider basic temporal patterns associated with muscles innervated from the sacral spinal segments in HSP. Overall, the applied methodology highlighted the impact of the corticospinal degeneration and spasticity on the coordination of distal limb segments and basic muscle modules associated with distal spinal segments.

1. Introduction

Assessing sensorimotor deficits specific to a disease is useful in defining targets for the rehabilitation therapies and motor recovery. Spastic gait is a key feature in patients with hereditary spastic paraparesis (HSP) and, even though HSP is primarily related to the degeneration of the corticospinal tract, it is a complex disease affecting different parts of the central nervous system (CNS) and impairing the functioning of spinal reflexes (Fink, 2013) and central pattern generators (CPG) (Martino et al., 2018). Furthermore, locomotion is a rather complex task that requires the coordination of multiple body segments in order to achieve dynamic stability without excessive energy expenditure (Bianchi et al., 1998b). The intersegmental coordination involves the synergistic activation of a large number of muscles, reflecting a great number of degrees of freedom needed to be controlled by the CNS. To address this complexity, the CNS relies on a modular architecture in which several pattern generators located within the spinal cord, under the influence of supraspinal signals and sensory feedback, control the rhythmic and alternating movements of the locomotion (Grillner, 2011; Kiehn, 2016). The coupled activity of these CPGs results in the activation of leg muscles and, consequently, in the kinematic coordination of lower limb segments (Lacquaniti et al., 2002). The progressive weakness and spasticity of the lower limbs in HSP (Klebe et al., 2015; Lo Giudice et al., 2014) may affect these biomechanical and neural mechanisms involved in the coordination of walking.

A variety of approaches have been adopted for assessing multi-joint coordination during different tasks (Ivanenko et al., 2008; Papi et al., 2015; Welch and Ting, 2009; Zhang et al., 2014). All these studies agreed with the idea that coordinative mechanisms lead to a reduction of the dimensionality of the degree of freedom of the motor control (Wang et al., 2013). In particular, several studies showed a high coupling and correlation of the lower limb segments during human locomotion (Grasso et al., 2000; Ivanenko et al., 2008). The pattern of intersegmental coordination may be described by studying the kinematic segmental covariation between thigh, shank and foot elevation angles,

* Corresponding author at: Wallace H. Coulter Dept. of Biomedical Engineering Emory University and Georgia Institute of Technology, Atlanta, GA 30322, USA.
E-mail address: giovanni.martino@emory.edu (G. Martino).

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Table 1
Patients' characteristics. A defined molecular diagnosis of HSP was applied to sixteen patients. Of these, ten patients had a spastic paraplegia (SPG) type four (mutation in SPAST), one patient had SPG3A (mutations in ATL1), one patient had SPG5 (mutations in CYP7B1), and three patients had SPG31 (mutations in REEP1). Five patients did not have a molecular diagnosis at the time of examination, but they unequivocally showed either a recessive (AR, three patients) or dominant (AD, two patients) inheritance pattern.

Patients	Age, yr.	Gender	Height, cm	Body Wt., kg	Diagnosis	SPRS	Onset, yr.	Duration, yr.
HSP1	23	F	170	64.7	AR	1	20	3
HSP2	21	F	163	58	SPG4	2	3	18
HSP3	43	M	172	86	SPG31	2	30	13
HSP4	47	F	159	61.5	SPG4	3	45	2
HSP5	25	M	180	85	AD	3	13	12
HSP6	62	M	161	83.5	SPG4	5	40	22
HSP7	66	F	154	57	SPG4	6	30	36
HSP8	47	M	174	87	SPG4	7	35	12
HSP9	43	F	162	57.5	SPG4	7	5	38
HSP10	24	M	177	104	SPG4	11	14	10
HSP11	56	M	164	75	SPG4	12	45	11
HSP12	64	F	158	61	SPG31	12	15	49
HSP13	28	M	181	80.8	SPG4	12	13	15
HSP14	48	M	170	88	AR	13	10	38
HSP15	28	M	165	69.2	AD	16	20	8
HSP16	57	F	156	65.5	SPG5	20	36	21
HSP17	49	M	182	109	SPG4	21	37	12
HSP18	72	F	149	77	SPG31	23	16	56
HSP19	58	M	170	72.5	SPG4	27	45	13
HSP20	39	M	186	136	SPG3a	27	20	19
HSP21	59	M	157	87	AR	28	30	29

known as the planar law of intersegmental coordination (Borghese et al., 1996). This law has been studied in several disorders related to the CNS (Cappellini et al., 2016; Chow and Stokic, 2015; Martino et al., 2014; Wallard et al., 2018), including a case report of a patient with HSP (Dan et al., 2000). In the latter study, Dan et al. showed that the shape and orientation of the loop defining the patient's planar covariation significantly differed from that of the controls and suggested that this was a consequence of the decreased inhibition of afferent terminals on motoneurons. The reduction of the motoneuron excitability using intrathecal baclofen injection could restore the normal control of phase coupling of lower limb segments (Dan et al., 2000). Despite the interest of this case study, a larger number of participants appear necessary to evaluate the intersegmental coordination in HSP.

Besides the characterization of the biomechanical features describing the coordinative patterns of walking, it is crucial to evaluate the changes in the neural control strategies caused by a lesion of the CNS. In the last two decades, electromyographic (EMG) studies have been performed and revealed few functional modules able to explain the activity from a large number of simultaneously recorded muscles through factorization algorithms in healthy participants (d'Avella et al., 2006; Dominici et al., 2011; Martino et al., 2015; Santuz et al., 2018). Moreover, a number of studies have evaluated the modular organization of the locomotor output in patients with CNS lesions associated with corticospinal dysfunction. Studies on post-stroke patients revealed an impaired control of muscle activity, though some discrepancies were reported about a reduction of modular complexity (Clark et al., 2010; Gizzi et al., 2011; Routson et al., 2014). Persons with multiple sclerosis showed a comparable structure in the modular organization of muscle activity, with some alterations in the activation timing profiles (Lencioni et al., 2016). Children affected by cerebral palsy also showed a similar modular structure, but specific impairments in the duration of basic activation patterns (Cappellini et al., 2016). While the experimental studies on individuals with CNS lesions have demonstrated distinct strategies of adaptation (Ting et al., 2015), the contribution of the corticospinal tract in the spinal locomotor pattern generation requires further investigations.

HSP involves primary retrograde degeneration of corticospinal fibers originating from many areas of the cerebral cortex, but mainly from the primary motor cortex and premotor frontal areas. A significant portion of the lateral corticospinal tract is involved in the control of the distal musculature of upper limbs (Lemon, 2008). Furthermore, the primary motor cortex (M1) influences ongoing EMG activity also of the lower limb muscles during gait (Barthélemy et al., 2011). Transcranial magnetic stimulation (TMS) studies revealed a large output from the motor cortex to the distal muscles around ankle joint (i.e. tibialis anterior muscle) and foot (i.e. abductor halluces muscle) (Kesar et al., 2018; Sivaramakrishnan et al., 2016). In a recent study, we found that the impairment of the corticospinal tract in HSP is associated with a widening of spinal motoneuronal activity spreading from caudal to rostral segments (Martino et al., 2018). To further investigate the coordinating patterns, here we examined the intersegmental coordination and the modular organization of EMG patterns. Due to the weakness and spasticity affecting the lower limbs, we expected that individuals with HSP would exhibit specific spatiotemporal characteristics of the locomotor output. In line with our previous findings (Martino et al., 2018; Serrao et al., 2016), we hypothesized a greater impairment at distal segments than proximal segments, also in relation with the pattern of innervation of spinal motoneurons by corticospinal fibers. We further hypothesized a prolonged activation of the muscle modules as a consequence of improper feed-forward and feedback processing resulting from the corticospinal degeneration. In healthy subjects, normal patterns of neuromuscular control consist in relatively brief, pulsatile activation of the lower limb muscles at critical times of the gait cycle, corresponding to limb extension at foot touch-down, body-weight support during stance, limb lift-off, and swing (Lacquaniti et al., 2012). Degeneration of corticospinal fibers might lead to a prolongation (widening) of these pulses of activation due to inefficient descending modulation of the activation timing and due to a compensatory mechanism of gait instability.

2. Methods

2.1. Study participants

We analysed the locomotor coordination in twenty-one individuals with HSP (8 females and 13 males; age 45.7 ± 15.8 yrs [mean ± SD]), and twenty healthy subjects (7 females and 13 males; 48.4 ± 10.9 yrs). The characteristics of patients are described in Table 1. All patients have undergone a clinical evaluation prior to taking part in the study. This consisted in the assessment of muscle

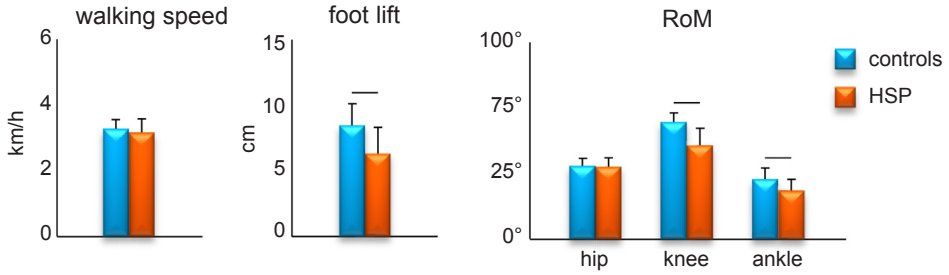

Fig. 1. General gait parameters for controls and HSP patients (mean + SD). RoM, range of motion. Horizontal lines denote significant group differences.

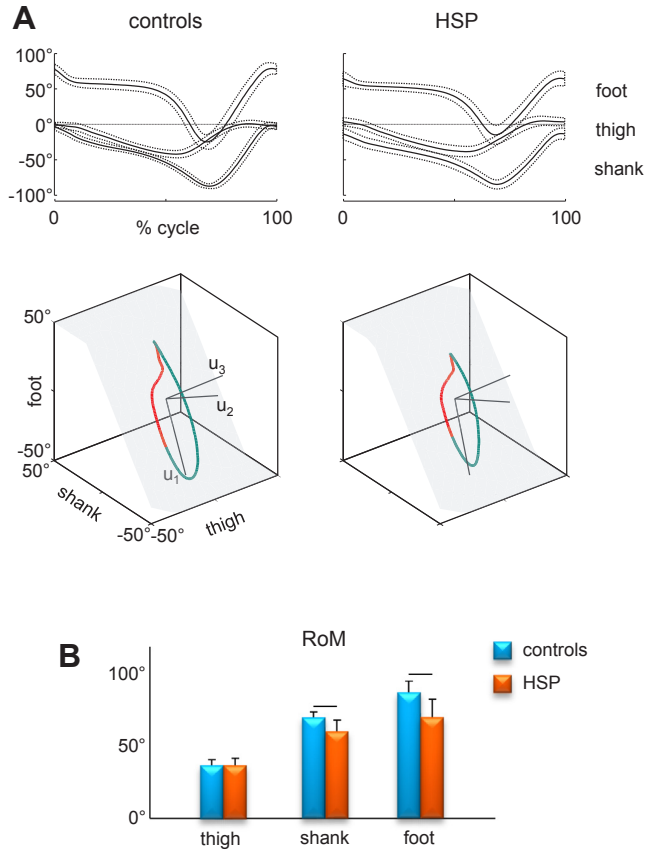

Fig. 2. Planar covariation of limb segment elevation angles. A: ensemble-averaged (across subjects) thigh, shank and foot elevation angles (mean ± SD) plotted vs. normalized gait cycle (upper panels) and corresponding 3D gait loops and interpolation planes (lower panels). Gait cycle paths progress in time in the counter clockwise direction (stance and swing phases in green and red, respectively). The interpolation planes result from orthogonal planar regression. The first (u_1), second (u_2) and third (u_3) eigenvectors of the covariation matrix are shown. B: Range of motion of elevation angles. Horizontal lines denote significant group differences. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tone, muscle strength, joint coordination, tendon reflexes, cranial nerves, and cognitive and sensory function. Furthermore, all patients undertook blood examinations and spine and brain MRI. Cortical evoked potentials (SEPs and VEPs) and nerve conduction studies (including F and H waves) were performed in those patients who suffered of visual or sensory disturbances. Since patients with complex genetic forms of HSP (SPG5, AD and AR) may suffer from symptoms other than corticospinal ones, we excluded those patients who exhibited gait disturbances that were not exclusively spastic in nature at the time of recordings. Patients were rated using the SPRS score (Schüle et al., 2006), in which higher scores indicate higher disease's severity. Only those that exhibited gait disturbances that were exclusively spastic in nature were included in the study. All participants were capable to walk independently, and they provided written informed consent to participate in this study, which had local ethics committee approval (Sapienza University of Rome, Policlinico Umberto I; Approval Number: UP 00259_2019) and complied with the Helsinki Declaration.

2.2. Experimental protocol and data collection

Each subject was asked to complete 15 walking trials, at comfortable self-selected speeds, along a 7 m walkway. Kinematics were recorded bilaterally at 300 Hz using an optoelectronic SMART-D motion analysis system (BTS, Milan, Italy) consisting of eight cameras with infrared strobes spaced around the walkway. Eight reflective spherical markers were bilaterally attached to the skin of the subjects overlying the following landmarks: fifth metatarsophalangeal joint (5MT), lateral malleolus, lateral femur epicondyle and greater trochanter.

The EMG data were recorded at 1000 Hz by means of a wireless FreeEMG300 system (BTS, Milan, Italy). The following 12 muscles were recorded on the right side of the body: gastrocnemius medialis (MG), gastrocnemius lateralis (LG), tibialis anterior (TA), peroneus longus (PL), soleus (SO), rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL), semitendinosus (ST), biceps femoris (long head, BF), tensor fascia latae (TFL) and gluteus medius (GM).

2.3. Kinematic analysis and intersegmental coordination

Heel strike and lift-off events were determined from the maximum and minimum excursions of the lower limb elevation angle (Borghese et al., 1996), defined as the angle between the whole limb segment (from greater trochanter to lateral malleolus) and the vertical axis. The steps related to gait initiation and termination were removed from the analysis and only those strides whose speed fell within the range of 2.5–4 km/h were retained for further analysis. Thus, we analysed the locomotor patterns at matched walking speeds. Also, the mean (± SD) number of analysed strides for HSP and control groups was similar: 13.8 ± 8.4 and 13.6 ± 7.9, respectively. The following general gait parameters were calculated: walking speed, foot lift and ranges of angular motion (RoM).

To assess the intersegmental coordination, a principal component analysis was applied to the covariance matrix of the time-varying limb segment elevation angles (thigh, shank, and foot), as previously described (Bianchi et al., 1998a; Borghese et al., 1996; Lacquaniti et al., 2002). Briefly, the eigenvalues and eigenvectors u_i, corresponding to the orthogonal directions of maximum variance in the sample scatter, were computed. The first two eigenvectors (u_1 and u_2) lay on the best-fitting plane of angular covariation and describe the global form of the gait loop, while the third eigenvector (u_3) is the normal to the plane and thus defines the plane orientation. The percentage of variance of the third principal component (PV_3) quantifies the planarity of the loop (for ideal planarity PV_3 = 0%). The percentage of variance demonstrated by the second component (PV_2) reflects the covariance loop width. To characterize the temporal changes of the two main principal

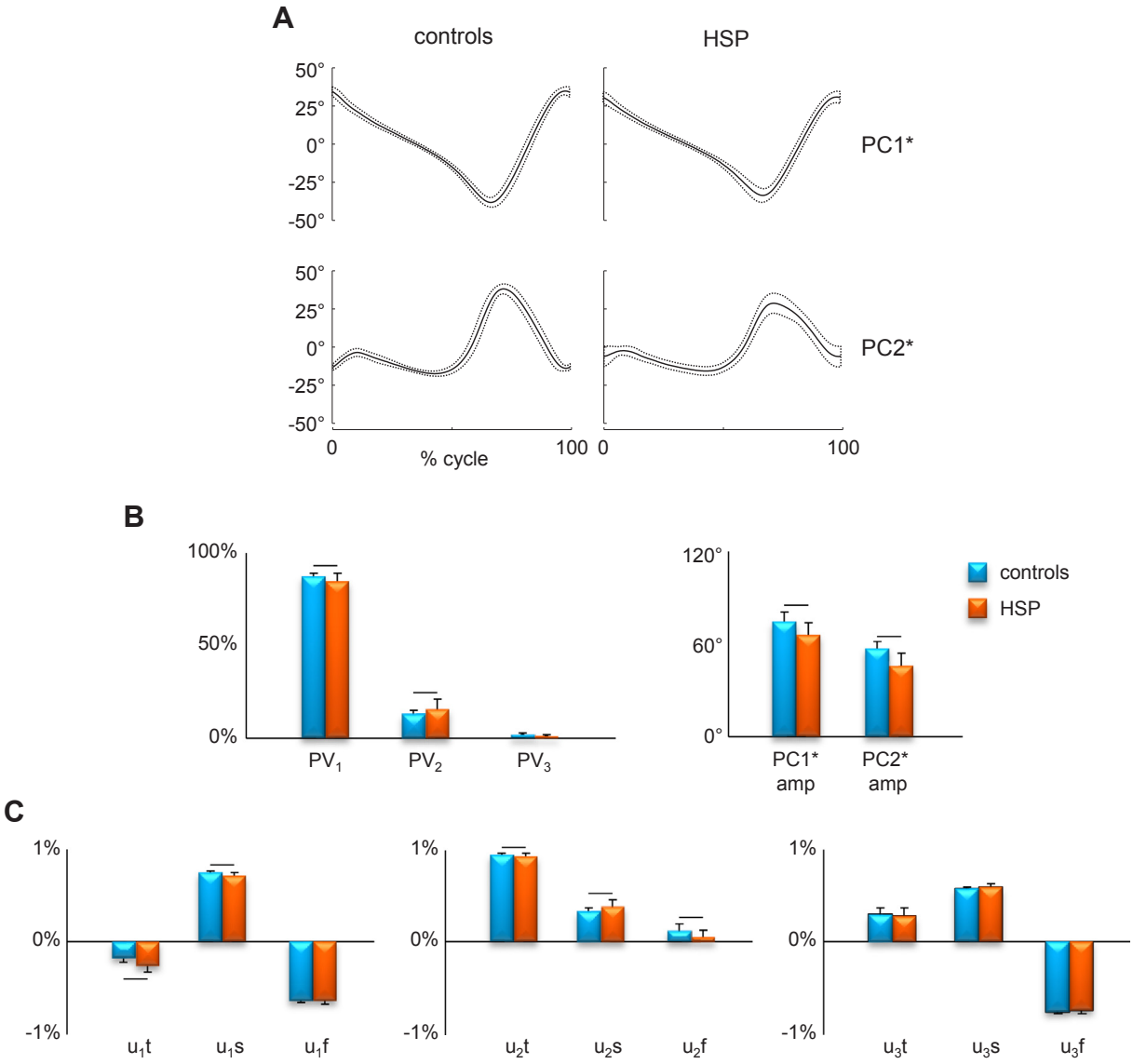

Fig. 3. Principal component analysis of limb segment elevation angles. A: ensemble averaged (mean ± SD) first (PC1*) and second (PC2*) principal components for each group. B: percent of total variation explained by first (PV_1), second (PV_2) and third (PV_3) principal component (left panel), and the peak-to-peak amplitude of PC1* and PC2*. C: direction cosines of the three eigenvectors of the covariation matrix (u_1 u_2 and u_3). t, thigh; s, shank; f, foot. Horizontal lines represent significant group differences.

components (PC1, PC2), we reoriented them to associate with the limb orientation and limb length changes (PC1*, PC2*). To this end, the orientation of the second axis PC2* was determined from a previous study (Ivanenko et al., 2007) in which subjects were walking in place: in this case, there was no change in the limb orientation and the covariance loop was a line that could be associated to the limb-length. The computed parameters of planar covariation were averaged across strides for each subject.

2.4. Motor modules

The raw EMG signals were pre-processed using demeaning, rectification and low-pass filtering at 10 Hz using a zero-lag fourth-order Butterworth filter. For each individual gait cycle, the time scale was interpolated over 200 points. The amplitude of each EMG signal was normalized to its peak across all trials for each subject. Motor modules were extracted using the NNMF algorithm, as previously described (Martino et al., 2015). Briefly, the processed EMG envelopes were combined into an $m \times t$ EMG matrix (where m is the number of muscles, and t is the number of gait cycles $\times$ *200*). Then, the NNMF algorithm extracts the basic activation patterns (P) and weighting coefficients (W) by searching for an approximate solution of the root-mean-squared error between the EMG matrix and $W \times P$, according to the formula:

$$EMG = \sum_{i}^{n} P_i W_i + error, \quad n \leqslant m \tag{1}$$

In order to determine the minimum number of modules that best accounts for the EMG data variance, we used the '*best linear fit*' method based on the percent of variance accounted for (*VAF*) (Martino et al., 2015). To identify and average similar basic patterns across subjects, the degree of similarity was evaluated based on the best-matching scalar product of both basic temporal patterns and weighting coefficients normalized to the Euclidean norm (Cappellini et al., 2016; Martino et al., 2015).

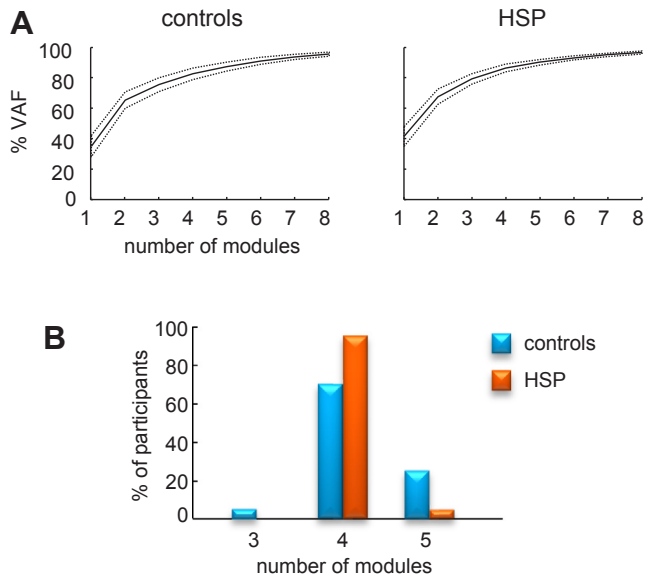

Fig. 4. Statistical analysis of EMG patterns. A: cumulative percent of variance (VAF) (± SD) accounted for by basic EMG components. B: number of modules needed to account for cycle-by-cycle variability. Even if three to five modules were sufficiently representative in a few participants, EMG activity in most subjects was well accounted for by four modules.

2.5. Statistics

Descriptive statistics included the calculation of the mean and SD. Wilcoxon signed rank test was used to compare groups. P-values < 0.05 were considered statistically significant. Between group similarities in muscle synergies were assessed by measuring the scalar product between them (after normalization to unit vectors). The duration of the basic temporal patterns was compared using the full width at half maximum (*FWHM*) parameter, defined as the sum of the durations of the intervals in which the basic patterns exceeded half of its maximum (Martino et al., 2015). Spearman rank correlation was used to calculate the statistical dependence with the clinical scores. All statistical analyses were performed using Matlab® (MathWorks Inc., MA, USA).

3. Results

3.1. General gait parameters

Fig. 1 shows general gait parameters. While we analysed the kinematic variables at matched walking speeds (Fig. 1), nevertheless HSP patients demonstrated systematic differences in lower limb behaviour with respect to the controls. In particular, we found a differential effect on proximal and distal joints' RoM. Whereas hip angle oscillations were similar ($p = 0.69$), HSP patients demonstrated a substantial decrease of the RoM of the knee and ankle joint angles ($p < 0.0001$ for both angles, Fig. 1 right panel). In addition, HSP patients showed a significant decrease of the foot ($5MT_z$) lift ($p = 0.0033$, Fig. 1 middle panel).

3.2. Intersegmental coordination

During human walking, limb segment rotations covary (Lacquaniti et al., 2002) and the coordination between leg segment elevation angles was evaluated using principal component analysis (Figs. 2 and 3). Fig. 2A illustrates the averaged thigh, shank, and foot elevation angles and corresponding gait loops plotted in 3D, the RoMs of the elevation angles being plotted in Fig. 2B. Note significantly smaller oscillations of the distal (shank and foot) segments in HSP patients (along with smaller RoM in the knee and ankle joints, Fig. 1). The time-changes of the elevation angles describe a loop (Fig. 2A lower panels) that lies close to a plane ($PV_3 < 1\%$; Fig. 3B).

Fig. 3 illustrates the characteristics of the limb segment planar covariation. The percentage of variance accounted for by the three PCs is plotted in Fig. 3B (left panel). Note that PV_1 was smaller while PV_2 was greater in HSP ($p < 0.049$ for both variables, Fig. 3B), indicating a more elongated loop in controls, while PV_3 was small ($< 1\%$) and similar for both groups. We also characterized the temporal changes of the two main principal components (Fig. 3A). PC1 and PC2 were re-oriented to be associated with the limb orientation (PC1*) and the limb length (PC2*) respectively (Ivanenko et al., 2007). The PC1* amplitude was smaller in HSP (Fig. 3B), corresponding to a relatively smaller leg swing. The PC2* amplitude was also reduced (Fig. 3B), consistent with the smaller changes in limb length and smaller foot lift in HSP (Fig. 1). The orientation of the covariation plane, quantified by the orientation of the normal to the plane (u_3) was similar (Fig. 3C), though the two principal components (u_1 and u_2, lying on the covariation plane) were slightly rotated in HSP (Fig. 3C), consistent with changes in the gait loop shape (Fig. 3B).

3.3. Motor modules

In both groups, the overall EMG activity changes during walking were adequately reconstructed by few motor modules (Fig. 4). Even if the EMG activity in most subjects was well accounted for by four modules, we did not constrain the number of modules for all subjects, but we individually identified the number of modules and then compared them across groups.

The basic activation patterns and muscle weights were extracted for each subject and then grouped based on the best similarities (see *2.4 Motor modules* in *Methods*). Unmatched modules were first identified and then pooled together as Not Classified (NC, Fig. 5A and B). The basic activation patterns are reported in Fig. 5A, while corresponding weights (muscle synergies) are reported in Fig. 5B. Pattern P1 was mainly loaded on the proximal muscle activity of knee extensors (VL, VM) and hip flexors (TFL, RF) during late swing and early stance to provide weight acceptance. Pattern P2 was primarily involved in loading and forward body propulsion consisting in the activation of the ankle plantar-flexor muscles (SOL, MG, LG, PL). Pattern P3 consisted mainly of TA activity for foot lift during swing. Pattern P4 was primarily related to the activity of the hamstrings (ST, BF) contributing to leg control and deceleration during late swing and early stance. Pattern P5 was loaded on several muscles and was found only in few subjects.

The characteristics of the common motor modules (P1-P4, W1-W4) are shown in Fig. 5C and D. The *FWHM* was significantly greater for P2 and P4 in the HSP group ($p < 0.0001$) (Fig. 5C), indicating a significant prolongation of the duration of these basic patterns. The muscle weights (W1–W4) in individuals of both groups were generally similar to the mean vectors of the control group (Fig. 5D): the mean scalar products for W1–W4 were 0.89 ± 0.09 for controls and 0.86 ± 0.11 for HSP. For W5, the mean scalar products were lower (not shown): 0.71 ± 0.21 for controls and 0.29 ± 0.29 for HSP. In sum, the EMG factorization analysis revealed a comparable structure of the motor output between groups (number of modules and similar synergies, Figs. 4 and 5B and D), but wider basic temporal activation patterns P2 and P4 in HSP (Fig. 5C).

3.4. Correlation with clinical scores

Fig. 6 shows the relationship between clinical SPRS measures and gait parameters. The following parameters correlated significantly with the SPRS score: shank RoM ($p = 0.002$), foot RoM ($p = 0.0008$), PC2* amplitude ($p = 0.008$), FWHM of P2 ($p = 0.03$). Thus, a large number of gait and muscle pattern parameters that were different between HSP and controls (Figs. 1–3 and 5) correlated with the severity of pathology (SPRS score).

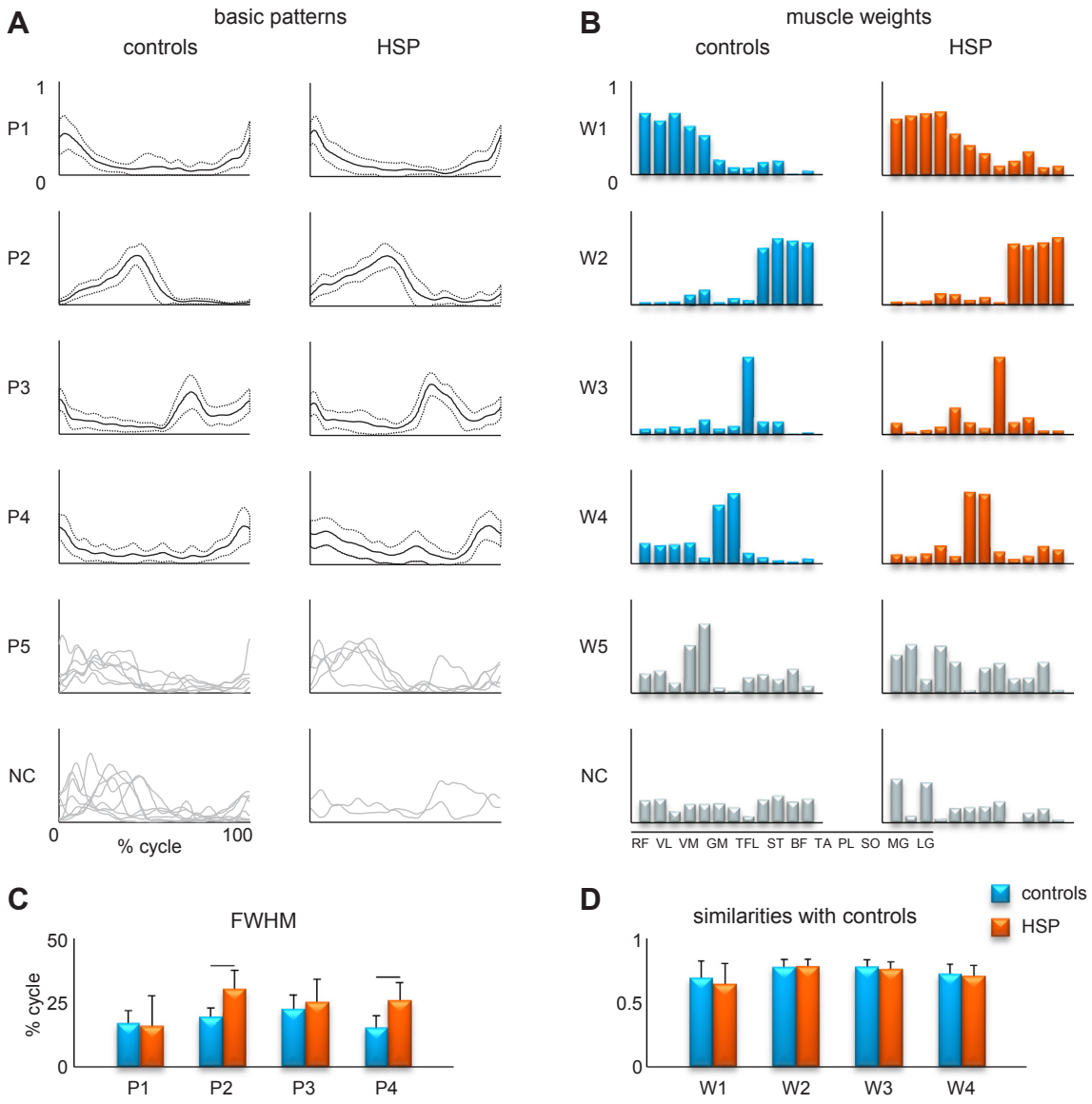

Fig. 5. Comparison of basic activation patterns and muscle weights. A: Common basic patterns (P1-P4) were plotted in a "chronological" order (with respect to the timing of the main peak). Each curve represents the mean (± SD, across subjects) pattern. Modules with low structural consistency across subjects (P5 and NC, not classified) were plotted separately on the bottom. B: corresponding group mean weights (synergies). C: mean (+SD) FWHM of basic activation patterns. D: similarities of weights. Horizontal lines denote significant differences.

4. Discussion

We investigated the intersegmental coordination and the changes in the modular structure of the locomotor output in a group of patients diagnosed with HSP. In particular, we found a remarkable differential effect on distal and proximal limb segment motion and muscle activity, namely a greater impairment at distal segments than proximal segments (Figs. 1, 2 and 5). There were also alterations in the shape of the loop of covarying elevation angles (Figs. 2 and 3). The EMG factorization analysis revealed a comparable structure of the module composition between groups, but wider basic temporal activation patterns in HSP (Figs. 4 and 5). The 'widening effect' consists in a prolongation of the muscle activity bursts as a consequence of improper feed-forward control and/or feedback processing, leading to inaccurate movements (Martino et al., 2014). Finally, many of these parameters correlated with the severity of disease (Fig. 6). The results highlight the importance of functional assessment of gait coordination to better understand the impact of the corticospinal degeneration and the role of this motor pathway for the neural control of movement.

The results suggest several physiological markers of gait impairment in HSP. In our previous studies (Martino et al., 2018; Serrao et al., 2016), we identified distinct groups of HSP patients based on the RoM of the hip, knee and ankle joints to help the clinical assessment in tailoring rehabilitative interventions. To avoid an effect of speed on gait kinematics, in this study we specifically focused our analyses on comparing gait at matched walking speeds in control subjects and HSP patients. Indeed, the difference in walking speeds between groups could represent a considerable confounding factor. Subjects walking at lower speeds would show a reduction in the joint range of motion. Here, we demonstrated that, even at matched walking speeds, the patients showed idiosyncratic kinematic characteristics (Fig. 1) that are correlated with the severity of the pathology (Fig. 6). In particular, we found that a distinctive feature of the HSP gait is a considerably smaller oscillation of the distal limb segments (shank and foot, Fig. 2, along with smaller RoM in the knee and ankle joints and a reduction of foot lift, Fig. 1), while the movements of the proximal thigh segment were essentially identical to those of controls.

The analysis of the intersegmental coordination revealed the planar

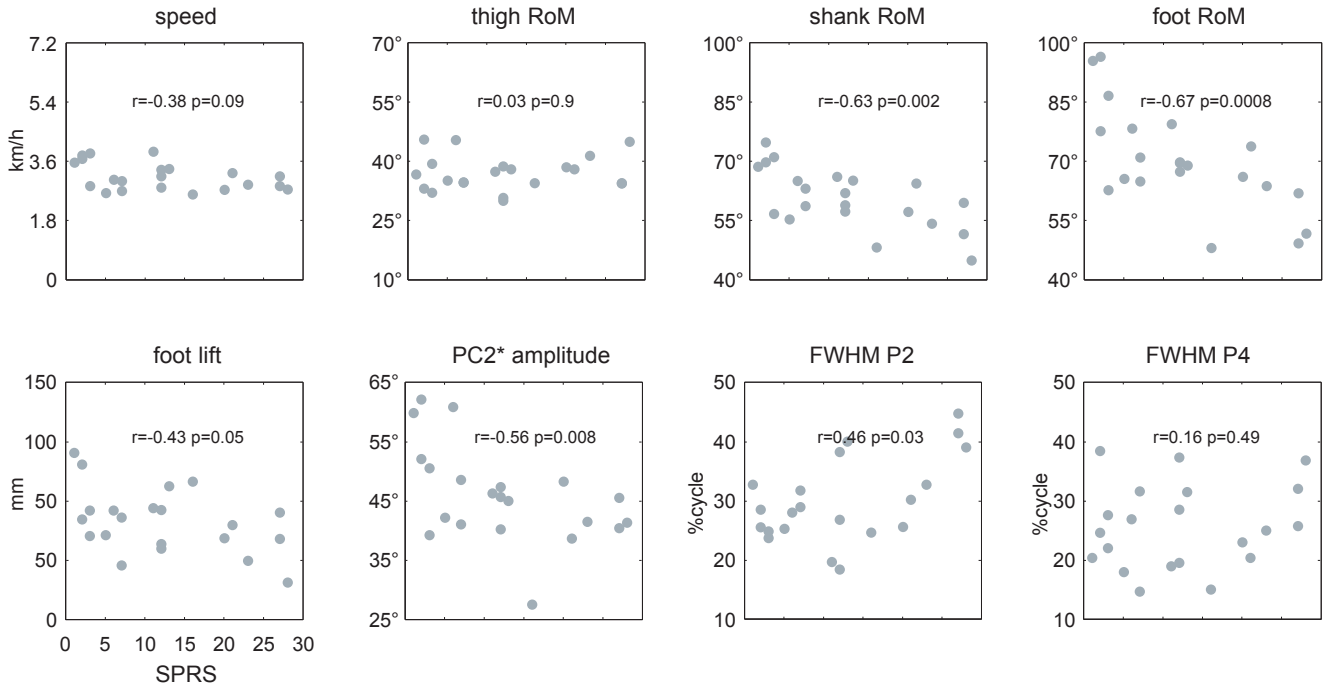

Fig. 6. Correlations between gait characteristics and the Spastic Paraplegia Rating Scale (SPRS). Each point represents the averaged (across strides) value for the individual patient. Correlation r and p values are reported.

covariation characteristics in HSP that are in agreement with the previous results reported in a case study (Dan et al., 2000). In particular, we found that planarity, represented by a small percentage of variance accounted for by the 3rd eigenvector, was also present in patients. Furthermore, the covariance plane was characterized by an abnormal shape of the loop (expressed by the higher values of PV_2 in patients, Fig. 2). In contrast to Dan et al., though, we did not find any significant difference in the orientation of the covariation plane, either because of intersubject variability in our data or because the patient reported by Dan et al. was not representative of a population. However, the impairments in the planar covariation confirm one main finding of Dan et al., namely the abnormal phasing between thigh, shank and foot angular motion that may be related to enhanced spinal reflexes due to decreased inhibition of afferent terminals on motoneurons (Dan et al., 2000) or impaired motor patterns (Martino et al., 2018). Another interesting feature of the HSP gait is a substantially reduced vertical foot lift (Fig. 1), associated with a smaller amplitude of the second principal component (Fig. 3A and B). These remarkable changes (~30% reduction in the foot lift, Fig. 1) could not be accounted for by the walking speed (since we matched it) or differences in the limb length since the anthropometric data were similar in HSP patients and controls.

The examination of motor patterns also showed specific characteristics of the HSP gait. To our knowledge, this is the first report of the modular organization of neuromuscular commands in HSP. We found that, in most patients and controls, four modules were sufficient to reconstruct the overall muscle activity (Fig. 4). The choice of the minimum number of motor modules needed by the NNMF model to reconstruct the original signals may be affected by various factors including filtering conditions, number of muscles, and/or adopted criterion (Hug et al., 2012; Steele et al., 2013; Zelik et al., 2014). Nevertheless, high similarities of basic patterns (Fig. 5A) and muscle synergies (weights, Fig. 5B) between the groups suggest that the emerging structure well describes our dataset. This result suggests that the weighting coefficients (muscle synergies) are not significantly influenced by a corticospinal dysfunction, at least in a group of patients with the SPRS score less than 30 (Table 1). In contrast, the activation profiles of basic patterns showed significant changes. Specifically, we found an increase in the duration of activity in patterns P2 and P4 (Fig. 5), in accordance with widening of spinal segmental activity (Martino et al., 2018). Since patterns P2 and P4 are loaded on the muscles innervated by the sacral spinal segments (PL, SO, MG, LG [P2] and ST, BF [P4] are innervated from S1 and S2 segments, (Sharrard, 1964), these findings further corroborate the idea that spasticity due to the degeneration of the corticospinal tract in HSP affects principally the distal (sacral) spinal motor pool functioning.

Overall, the findings highlight specific impairments in the HSP gait. The applied methodology allowed to uncover the effect of the corticospinal degeneration and spasticity on the coordination of distal limb segments and basic muscle modules associated with distal spinal segments. Lower extremity spasticity and weakness are considered the primary cause of gait disturbances in patients with HSP (Fink, 2013). In this study, the observed widening of basic patterns may reflect some common physio-pathological mechanisms related to the spasticity and leading to an increase of the muscle co-contraction (Rinaldi et al., 2017). The delay between an acute neurological insult (e.g., after stroke or trauma) and the appearance of spasticity suggests some sort of plastic changes occurring in the spinal cord and the motor cortex. These alterations disrupt the balance of supraspinal inhibitory and excitatory inputs directed to the spinal cord (Trompetto et al., 2014). A decreased cortical inhibition after lesion or degeneration of corticospinal tract, may be bypassed by brain stem extrapyramidal pathways such as vestibulospinal, reticulospinal, and tectospinal tracts, which project more extensively to spinal motoneurons controlling movements of proximal, rather than of distal parts of the limbs (Jankowska and Edgley, 2006; Keizer and Kuypers, 1984; Riddle et al., 2009). Furthermore, a series of plastic changes might occur at the level of spinal cord neurons and interneurons as observed in animal models after corticospinal lesions (Oudega and Perez, 2012). Such modification, thereby inducing the abnormal patterns of muscle contraction (Kamper and Rymer, 2001) and loss of selectivity in muscle recruitment (Martino et al., 2018; Serrao et al., 2016). Thus, although the compensation from the parallel descending pathways, these pathways are not capable of generating fine, skilled movements, resulting in more coarse movements. Impaired corticospinal influences, associated with a deficient modulation of

spinal interneuronal circuits, may lead to defective use of segmental motor pools, contributing to the abnormal locomotor pattern. Such knowledge about determinants in the physiopathology of spastic gait might be essential to focus the rehabilitative treatment, for instance, a selective treatment of spinal circuitry to restore the functioning of locomotor pattern generators (Solopova et al., 2017; Wenger et al., 2016).

Conflict of interest

The authors declare that they have no conflict of interest related to this work.

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Giovanni Martino is a Postdoctoral Fellow at Wallace H. Coulter Department of Biomedical Engineering, Georgia Tech College of Engineering and Emory School of Medicine. After receiving the M.S. degree in Bioengineering at the University of "Roma Tre", he completed the PhD Program in Neuroscience at the University of Rome "Tor Vergata" and in collaboration with the laboratory of Neuro-Motor Physiology at the Scientific Institute Santa Lucia Foundation (Rome). His research interests are largely directed towards understanding the neural control and the biomechanics of human movement in both normal and pathological conditions.

Yury Ivanenko is a Research Director at the Laboratory of Neuro-Motor Physiology at IRCSS Santa Lucia Foundation, leader of the Gait and Posture team. He obtained his M.S. degree in Biophysics at Moscow Physics and Technology Institute in 1982 and Ph.D. in Biophysics under the supervision of Victor Gurfinkel working at the Institute for Information Transmission Problems, Russian Academy of Sciences. He was a lecturer in Biophysics and Biochemistry at the Ryazan Medical Institute and did a post-doc with Alain Berthoz at Collège de France in Paris. His main interest is investigation of normal and pathological human gait, sensorimotor interactions, early development of locomotion, spinal cord neurophysiology and pattern generation circuitry. He is at IRCCS Fondazione Santa Lucia since 1998.

Mariano Serrao is an Assistant Professor at the Department of Surgical and Medical Sciences and Biotechnologies, "Sapienza" University of Rome, Polo Pontino and a consultant Neurologist of the Rehabilitation Unit, ICOT – Rehabilitation Institute, Latina, Sapienza University of Rome, Polo Pontino, Italy. He received degree in Medicine with honors from Sapienza University of Rome in 1995, post-graduate Specialization in Neurology with honors from Sapienza University of Rome in 1999 and PhD in Neuroscience, Motor Rehabilitation and Behavioral Science from Sapienza, University of Rome in 2003. He authored more than 160 publications in international and national journals. His main fields of research are: neurophysiology; movement disorders; movement analysis; nociception.

Alberto Ranavolo received the MSc degree in Electronic Engineering at Federico II University of Naples and PhD in Rehabilitation Medicine at Sapienza University of Rome, is Researcher at the Department of Occupational and Environmental Medicine, Epidemiology and Hygiene of INAIL, the Italian Workers' Compensation Authority. His main research interests are human factors and ergonomics, job accommodation, clinical biomechanics, neurophysiology, movement disorders and movement analysis. He is dedicating special attention to instrumental-based techniques for the biomechanical risk assessment in lifting activities and repetitive movements. Furthermore, he is focusing his interest on "back to work" of workers affected by several musculoskeletal disorders. He is author of about 50 scientific papers in international peer-review journals. He currently is professor at the University's Master in Neurorehabilitation at Sapienza University of Rome, is in the Editorial Committee and serves as reviewer for many journals in the area of biomedical engineering.

Francesco Draicchio works at Department of Occupational and Environmental Medicine, Epidemiology and Hygiene of INAIL, the Italian Workers' Compensation Authority (Monte Porzio Catone, Italy.) He is head of Ergonomics and Physiology Laboratory of INAIL. He received degree in Medicine (1986) from Catholic University of SH of Rome, PhD in Neuroscience (1990) from Catholic University of SH of Rome, Specialization in Occupational Medicine (1993) from Catholic University of SH of Rome, CREE Master in Ergonomics (2003) from Italian Society of Ergonomics and Specialization in Aviation Space and Environmental Medicine (2005) from Sapienza University of Rome. His fields of expertise & research interests: Work-Related Musculoskeletal Disorders and Physical Ergonomics.

Carlo Casali is an Associate Professor at the Department of Surgical and Medical Sciences and Biotechnologies, "Sapienza" University of Rome, Polo Pontino and a consultant Neurologist of the Rehabilitation Unit, ICOT – Rehabilitation Institute, Latina, Sapienza University of Rome, Polo Pontino, Italy. He received degree in Medicine with honors from Sapienza University of Rome in 1980, post-graduate Specialization in Neurology with honors from Sapienza University of Rome in 1984 and PhD in Neuroscience from Catholic, University of Rome in 1989. He authored more than 250 publications in international and national journals. His main fields of research are: neuromuscular and neurodegenerative disorders, neurogenetics.

Francesco Lacquaniti received both an M.D. and a specialty in Neurology from the Medical Faculty of Turin University. After a post-doc in the Department of Physiology of the University of Minnesota in Minneapolis, he joined the Italian National Research Council in Milan where he was Acting Director of IFCN until 1994. In 1994 he became full professor of Physiology at Cagliari University and, since 1997, he holds the same position in the Medical Faculty of the University of Rome Tor Vergata. He is the director of the Centre of Space Bio-medicine at the same University and the director of the Laboratory of Neuro-Motor Physiology at the Scientific Institute Santa Lucia Foundation (Rome). He has been elected to the Academia Europaea and received the Herlitzka Prize for his discoveries in the field of motor control.