

POLITECNICO DI MILANO  
Scuola di Ingegneria dei Sistemi  
Corso di Laurea Magistrale in Ingegneria Biomedica



TESI DI LAUREA MAGISTRALE

**Voluntary cycling augmented by functional  
electrical stimulation in hemiparetic adolescents:  
a case series study**

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Anno Accademico 2012-2013



*Ai miei genitori*



## *Ringraziamenti*

*La prima sensazione pensando a quante persone hanno contribuito al raggiungimento di questo traguardo è che queste pagine potrebbero continuare all'infinito.*

*In primo luogo vorrei ringraziare la Prof.ssa Alessandra Pedrocchi che mi ha dato l'opportunità di lavorare in un ambito appassionante aiutandomi a porre le basi per il mio futuro professionale. Un ringraziamento particolare va alla Dott. Emilia Ambrosini che, con competenza, pazienza ed attenzione mi ha seguito in questi mesi non facendomi mai mancare il suo sostegno. La mia gratitudine va anche alla Dott. Simona Ferrante che è stata sempre pronta a darmi preziosi consigli e che, soprattutto durante la splendida esperienza all'IFESS, è stata fonte di ispirazione.*

*Desidero ringraziare inoltre la Dott. Emanuela Pagliano e tutto il suo staff per la arricchente collaborazione durante questi mesi.*

*Oltre alle persone che mi hanno guidato nel lavoro, un grazie a chi mi è stato accanto in laboratorio, in particolare ad Elena, Noelia, Andrea e Cristina, che hanno reso divertente ogni giorno trascorso insieme e sono sempre state pronte ad aiutarmi.*

*Un pensiero ai molti amici vecchi e nuovi che mi hanno accompagnato in tutti questi anni. In particolare vorrei ringraziare Chiara, che mi sta accanto da tempi immemori, Cristina, con la quale ho imparato a studiare e ho passato le mie prime (e ultime!) notti ripetendo lezioni, e Giulia, la mia compagna di risate che, ovunque siamo, mi fa sempre sentire bene.*

*Forse un solo grazie non basta per Simone, che in tutto questo tempo ha saputo incoraggiarmi e stimolarmi senza mai farmi mancare il suo appoggio. Con te accanto tutto è stato più semplice e bello. Non posso dimenticare inoltre Sandra, Rosario e tutta la famiglia che in questi anni mi ha accolta e fatta sempre sentire a casa.*

*Infine tutta la mia gratitudine va a coloro che più di tutti hanno sostenuto il mio cammino, a voi mamma, papà, Marghi, nonna e zii. In modi diversi, chi con torte stracolme di amore, chi con affetto costante e dedizione, chi con quotidiana sopportazione, avete reso possibile questo percorso e avete saputo accompagnarmi fino a qui. A voi va gran parte del merito di ogni mio traguardo.*



## Sommario

### Stato dell'arte e obiettivi

Il presente lavoro è focalizzato sulla verifica dell'efficacia riabilitativa di un trattamento di pedalata volontaria aumentata da stimolazione elettrica funzionale (SEF) in adolescenti emiparetici.

L'emiparesi è una condizione patologica caratterizzata da una perdita parziale di funzionalità motoria indotta da danni cerebrali o midollari, tra cui icuts, paralisi cerebrale (PC) e traumi. Essa si manifesta con spasticità e debolezza muscolare, danneggiando le funzioni fino e grosso-motorie tanto da rendere difficile lo svolgimento delle attività quotidiane quali il cammino.

La PC e l'ictus sono tra le principali cause di emiparesi in soggetti giovani.

La PC è un gruppo di disordini motori che compare nei primi anni di vita ed è caratterizzata da un danno cerebrale non progressivo. I fattori di rischio più rilevanti sono la nascita prematura e sottopeso; alcuni studi recenti hanno verificato che l'incidenza di PC è in crescita nel mondo occidentale poichè il tasso di mortalità infantile è diminuito. Tra la popolazione affetta da PC, il 20-30% è interessato dalla forma emiplegica mentre la maggioranza dei soggetti presenta diplegia.

L'ictus è una patologia che comporta perdite di funzionalità neurologiche a causa di disturbi del flusso sanguigno nei vasi cerebrali che comportano ipo-ossigenazione dei tessuti.

La stimolazione elettrica neuromuscolare sta diventando un metodo convenzionale per la riabilitazione motoria in soggetti con disturbi neurologici poichè riduce i tempi di recupero ed inoltre, in alcuni casi, mantiene nel tempo i benefici.

In particolare la stimolazione elettrica funzionale (SEF) è largamente utilizzata perchè è volta al recupero di movimenti funzionali.

Il principio neurofisiologico su cui si basa è la generazione di potenziali d'azione nei motoneuroni inferiori grazie all'applicazione di impulsi di corrente elettrica. Tali impulsi vanno ad stimolare i nervi e i muscoli e, qualora venga raggiunta la soglia di eccitazione, provocano una contrazione muscolare.

La stimolazione può essere modulata attraverso alcuni parametri: la forma d'onda (monofasica o, più spesso, bifasica), la frequenza, l'ampiezza e la pulse width.

L'efficacia riabilitativa della SEF è stata dimostrata da molti studi [1], [2], [3] che testimoniano un miglioramento della forza, dell'atrofia muscolare, del ritorno venoso e del sistema cardiovascolare in genere. Sono inoltre stati osservati benefici nella riorganizzazione del movimento volontario e funzionale.

La SEF incrementa l'attività a livello dei circuiti corticali e spinali agendo sulla neuroplasticità e, conseguentemente, sul recupero motorio sia a breve che a lungo termine [4]. Questo effetto è massimizzato se la SEF è sincronizzata con il comando volontario.

Alcuni studi [5] hanno permesso di osservare una maggiore flessibilità del sistema nervoso centrale in soggetti giovani che, a parità di danno, ottengono un recupero delle funzioni motorie superiore. Malgrado le premesse incoraggianti, solo pochi studi hanno verificato l'effetto di trattamenti di SEF sulla neuroplasticità dei bambini.

Inoltre nella clinica si è osservato un ulteriore incremento della neuroplasticità tramite esercizi ripetitivi e orientati ad uno specifico obiettivo. Questo approccio può essere garantito in modo sicuro ed economico da trattamenti basati su pedalata indotta da SEF che, non richiedendo equilibrio, permettono di svolgere l'esercizio in sicurezza anche per pazienti con scarsa autonomia. La pedalata può essere d'aiuto anche nel recupero del cammino, che è uno degli obiettivi primari in soggetti con deficit motori. Infatti i due gesti motori della pedalata e del cammino hanno pattern cinematici simili essendo entrambi ciclici, con movimenti reciproci di flessione ed estensione che coinvolgono l'alternarsi dell'attivazione di muscoli agonisti/antagonisti in modo coordinato.

La strumentazione richiesta per un trattamento di pedalata indotta da SEF comprende un ciclo-ergometro sensorizzato e uno stimolatore che invia gli impulsi elettrici ad elettrodi di superficie opportunamente posizionati sui muscoli bersaglio. Tra questi i più utilizzati sono flessori ed estensori di ginocchio (quadricipite e hamstring), estensori dell'anca (gluteo massimo) e, a volte, dorsi-plantar flessori (tibiale anteriore e muscolo tricipite della sura). Una delle strategie di stimolazione più promettenti prevede di attivare ciascun muscolo nei range angolari di attivazione muscolare fisiologica, ottenuti su soggetti sani in uno studio precedente [6].

Negli ultimi anni, mentre le applicazioni di pedalata indotta da SEF nella riabilitazione



dell'arto inferiore di soggetti emiparetici adulti sono aumentate dimostrando l'efficacia del trattamento nel migliorare il recupero motorio, solo pochi studi sono stati effettuati sulla popolazione giovane [7].

La fattibilità del trattamento su 5 adolescenti affetti da PC è stata studiata recentemente [8] verificando che la stimolazione elettrica è ben tollerata dai pazienti. Un'altra ricerca [9] ha sottoposto a 21 sessioni di pedalata indotta da SEF due adolescenti con PC ottenendo miglioramenti di termini di simmetria del movimento e co-contrazione di muscoli agonisti-antagonisti. Inoltre uno studio randomizzato [10] su 62 bambini emiparetici ha dimostrato che un trattamento di pedalata standard (non assistito da SEF) non migliora significativamente il recupero motorio su giovani emiparetici. Pertanto la SEF aumentando la propriocezione potrebbe indurre benefici maggiori dei trattamenti di pedalata tradizionali.

L'obiettivo primario della presente tesi è di verificare la fattibilità e l'efficacia di un trattamento di pedalata volontaria aumentata da SEF nel migliorare il cammino e la funzionalità motoria dell'arto inferiore di adolescenti emiparetici. Al fine di monitorare i pazienti sono stati svolti alcuni test verificando le condizioni cliniche, l'abilità nel cammino e la performance in pedalata dei soggetti. Il presente lavoro è focalizzato sull'acquisizione e l'analisi dati del test di pedalata, mentre i dati clinici e di analisi del cammino sono stati raccolti ed analizzati per ottenere un quadro completo degli effetti del trattamento.

### **Materiali e metodi**

Sei pazienti sono stati reclutati presso l'Istituto Neurologico "C. Besta". I seguenti criteri di inclusione sono stati stabiliti per lo studio: età tra i 10 e i 18 anni, diagnosi di emiparesi acquisita, possibilità di cammino autonomo, bassi livelli di spasticità (scala di Ashworth modificata  $< 2$ ), mancanza di limitazioni articolari. I soggetti sono stati esclusi dalla sperimentazione nel caso fossero stati precedentemente trattati con tossina botulinica o avessero subito interventi di chirurgia. Inoltre si sono verificati l'assenza di allergia agli elettrodi e la tolleranza alla stimolazione elettrica. Vista la giovane età dei soggetti, era richiesta collaborazione da parte delle famiglie che hanno firmato un consenso informato. Il comitato etico dell'Istituto Besta ha approvato il protocollo di ricerca.

Tutti i partecipanti sono stati sottoposti al trattamento 3 volte a settimana per sette settimane, con sessioni della durata di 30 minuti. Ciascuna sessione comprendeva 5 minuti di

pedalata generata dal motore del ciclo-ergometro (fase passiva di riscaldamento), 20 minuti di pedalata volontaria sincronizzata con SEF, e ulteriori 5 minuti di pedalata passiva. Quattro muscoli (quadricipite, gluteo massimo, hamstring e tibiale anteriore) per ciascuna gamba sono stati stimolati in intervalli angolari sfasati di  $180^\circ$ . La strumentazione usata comprendeva uno stimolatore RehaStim (Hasomed GmbH) ed un ciclo-ergometro MOTO-med Viva2 (Reck GmbH).

Per verificare l'efficacia del trattamento i soggetti sono stati testati in quattro differenti sessioni, due prima del trattamento e due dopo. In particolare le prime due, nel seguito indicate come oPRE (observational-PRE) e PRE, erano a distanza di sette settimane durante le quali i soggetti hanno svolto le loro attività quotidiane. In questo periodo di osservazione è stato monitorato il trend di aggiustamento neuromotorio dovuto alla crescita. Le due sessioni successive al trattamento, indicate nel seguito come POST e FU (follow-up), erano distanziate di 12 settimane e hanno permesso di monitorare gli effetti del trattamento a breve e lungo termine.

Ciascuna delle quattro sessioni era composta da tre differenti tipologie di test: test clinici, analisi del cammino e test della pedalata.

I test clinici sono stati effettuati presso l'Istituto Neurologico "Carlo Besta" ed erano basati sull'analisi di scale ciniche neurofunzionali tra cui la classificazione di Winter per definire l'entità del deficit funzionale del cammino, la Gross Motor Function Measure (GMFM) per valutare cambiamenti in diverse funzioni grosso-motorie, il Test di Boyd per valutare il controllo volontario motorio selettivo distale e la Observational Gait Scale (OGS) che valuta i pattern cinematici del movimento durante il cammino. Infine la scala di Ashworth modificata ha permesso di classificare la spasticità dei soggetti.

L'analisi del cammino è stata realizzata presso il Laboratorio di analisi della postura e del movimento "Luigi Divieti" del dipartimento di elettronica informazione e bioingegneria (DEIB) del Politecnico di Milano al fine di ottenere informazioni quantitative su possibili benefici nel controllo motorio durante la locomozione. Su ciascun soggetto sono stati posizionati dei marker secondo il protocollo Davis ed è stato utilizzato il sistema optoelettronico ELITE 2000 (BTS company SpA, con 8 telecamere a frequenza di 100 Hz) integrato con due piattaforme di forza permettendo di estrarre informazioni circa i parametri spazio-temporali (la velocità media, la lunghezza del passo sia dell'arto paretico che

sano e un indice di simmetria calcolato come rapporto tra la lunghezza del passo paretico e di quello sano), la cinematica (angoli articolari di anca, ginocchio e caviglia sui piani frontale, sagittale e orizzontale), la cinetica (momento e potenza prodotti da caviglia, ginocchio e anca sul piano sagittale) e le forze verticali di reazione al terreno.

L'analisi della performance durante la pedalata è stata svolta presso il Laboratorio di Neuroingegneria e Robotica Medica (NEARLab) del DEIB del Politecnico di Milano. Il test è stato ritenuto particolarmente interessante perchè studia il compito motorio direttamente allenato durante il trattamento di SEF ed è consistito in 1 minuto di pedalata passiva e 2 minuti di pedalata volontaria in cui si era richiesto a ciascun paziente di mantenere la velocità a 30 rivoluzioni per minuto (rpm). Durante il test si è utilizzato un cicloergometro motorizzato (Thera-Live<sup>TM</sup>, Medica Medizintechnik GmbH, Germany), personalizzato con strain gauges montati su ciascun pedale per misurare il momento esercitato dalle due gambe durante la pedalata. L'angolo alla pedivella e il momento sono stati acquisiti con una frequenza di 200 Hz tramite PC con sistema operativo Linux e applicazione Real Time. Inoltre, grazie ad un sistema multi-canale di amplificazione del segnale (Porti32<sup>TM</sup> TMSi, Netherlands), durante la pedalata è stato acquisito con frequenza di 1 kHz il segnale elettromiografico (EMG) di retto femorale (RF), vasto mediale (VM), bicipite femorale (BF), tibiale anteriore (TA) e gastrocnemio mediale (GM) di entrambe le gambe tramite elettrodi di superficie bipolari. Il posizionamento degli elettrodi è stato definito seguendo le raccomandazioni di SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) in modo da minimizzare il crosstalk tra i segnali muscolari.

Durante ciascuna sessione una prova isometrica di massima contrazione volontaria (MVC) per ciascun muscolo è stata registrata in modo da avere informazioni circa il livello di massima attivazione muscolare per ciascuna sessione e di poter così confrontare i dati di differenti sessioni. È importante sottolineare che non è stato dimostrato in via definitiva che il valore di attivazione ottenuto rappresenti il massimo impulso neurale raggiungibile durante la pedalata.

Le misure estratte dal test di pedalata comprendevano la velocità mantenuta durante la fase di pedalata volontaria, il lavoro meccanico prodotto da ciascuna gamba, lo sbilanciamento tra le due gambe, i tempi e il livello di attivazione muscolare.

Il lavoro prodotto da ciascuna gamba è stato calcolato a partire dalle misure dei sensori

di forza montati sulle due pedivelle. In particolare si è ottenuto il profilo del momento “attivo” sottraendo dal momento registrato dai sensori in fase di pedalata volontaria, il profilo registrato durante la fase passiva. Il lavoro per ciascuna rivoluzione è stato quindi calcolato come integrale del profilo attivo in funzione dell’angolo alla pedivella per la gamba paretica ( $W_{PL}$ ) e quella sana ( $W_{HL}$ ). Il lavoro è stato ulteriormente analizzato separando il contributo prodotto spingendo e tirando il pedale ( $W_{PUSH}$   $W_{PULL}$  rispettivamente). Infine, una misura dell’asimmetria nel lavoro sviluppato è stata ottenuta grazie all’indice di sbilanciamento (o Unbalance) calcolato come  $U = \frac{|W_{HL}-W_{PL}|}{W_{HL}+W_{PL}}\%$ .  $U$  assume valori tra 0% (se i due lavori sono identici) e 100% ( $W_{PL}=0$ ).

La tempistica di attivazione muscolare e la co-contrazione di retto e bicipite femorale sono stati studiati a partire dal segnale elettromiografico. Dopo un filtraggio standard di condizionamento del segnale elettromiografico (filtraggio passa alto a 10 Hz, rettificazione e filtraggio passa basso a 5 Hz), il profilo di attivazione di ciascun muscolo è stato estratto come segue:

1. Interpolazione tramite spline per definire l’involuppo EMG in funzione dell’angolo alla pedivella. Le rivoluzioni che distano dalla media complessiva di più di 3 deviazioni standard sono state considerate outlier e rimosse.
2. Media ogni 20 secondi di acquisizione dei rimanenti profili ottenendo circa 6 profili medi nei 2 minuti di acquisizione.
3. Normalizzazione di ciascuno dei profili medi seguendo due differenti metodi. Il primo utilizza il valore massimo di tutti i 6 profili medi. Il secondo considera i valori acquisiti durante il test di MVC. Questo approccio è stato seguito solo per quei soggetti che sono stati in grado di eseguire, durante tutte le quattro sessioni del test della pedalata, l’MVC di tutti i muscoli con valori superiori a quelli registrati durante la pedalata volontaria. In questo modo è stato possibile confrontare i livelli di attivazione tra differenti sessioni.

La co-contrazione tra retto femorale e bicipite femorale è stata valutata usando un indice (CCI) definito in uno studio precedente [9]. In particolare il CCI per ciascun profilo medio è stato calcolato come  $CCI(j) = \frac{S_{Overlap}(j)}{S_{RF}(j) + S_{BF}(j)}$  con  $S_{RF}$  e  $S_{BF}$  che rappresentano l’area sottostante i profili EMG di retto e bicipite femorale normalizzati per il loro massimo

mentre  $S_{overlap}$  è l'area di sovrapposizione tra i due profili.

I range di normalità relativi al test della pedalata sono stati calcolati su un gruppo di sei coetanei sani (età  $14.3 \pm 1.0$  anni).

Infine è stata condotta un'analisi statistica dei risultati. In particolare il test di Kruskal-Wallis è stato utilizzato per confrontare variazioni nel tempo dei risultati del test del cammino e della pedalata. Qualora differenza significativa ( $p < 0.05$ ) fosse osservata tra oPRE, PRE, POST e FU, un'analisi post-hoc ha permesso di confrontare coppie di tests. Inoltre, un U-test di Mann-Whitney ha permesso di comparare i risultati di ciascuna sessione del test di pedalata con i valori del gruppo di controllo dei sani.

Nessun confronto tra soggetti patologici è stato effettuato per la bassa numerosità del campione analizzato.

## Risultati

Sei soggetti emiparetici sono stati reclutati dall'Unità di Neurologia dello Sviluppo dell'Istituto "C. Besta" ma due di essi hanno interrotto lo studio durante la seconda settimana del trattamento SEF a causa di un'eccessiva richiesta di impegno, non compatibile con i loro impegni quotidiani. Pertanto il trattamento è stato concluso da 4 soggetti di sesso maschile ed età compresa tra i 12 e i 17 anni con diagnosi di emiparesi acquisita (nel seguito indicati come S1, S2, S3 e S4). In particolare tre di loro erano affetti da paralisi cerebrale mentre il quarto (S4) ha subito un ictus ischemico 8 anni prima dell'inizio dello studio.

I test clinici hanno mostrato che i pazienti presentavano solamente una lieve disabilità durante oPRE e PRE tests. Infatti tutti i punteggi ottenuti erano appena inferiori ai range di normalità a parte il livello di spasticità che indicava la presenza di tono da moderato a severo. A seguito del trattamento le scale cliniche hanno mantenuto il valore iniziale.

Un esempio dei risultati principali ottenuti da uno dei soggetti (S4) durante l'analisi del cammino e il test della pedalata sono mostrati in Fig. 1.

L'analisi del cammino ha permesso di osservare che i soggetti erano in grado di camminare ad una velocità appena inferiore ai range di normalità. Secondo un recente studio [11], i valori di velocità ottenuti sono caratteristici di persone senza limiti sostanziali nelle attività quotidiane. La lunghezza del passo sia per l'arto paretico che per quello sano presentava qualche lieve deviazione durante oPRE e PRE, mantenute dopo il trattamento. Anche le

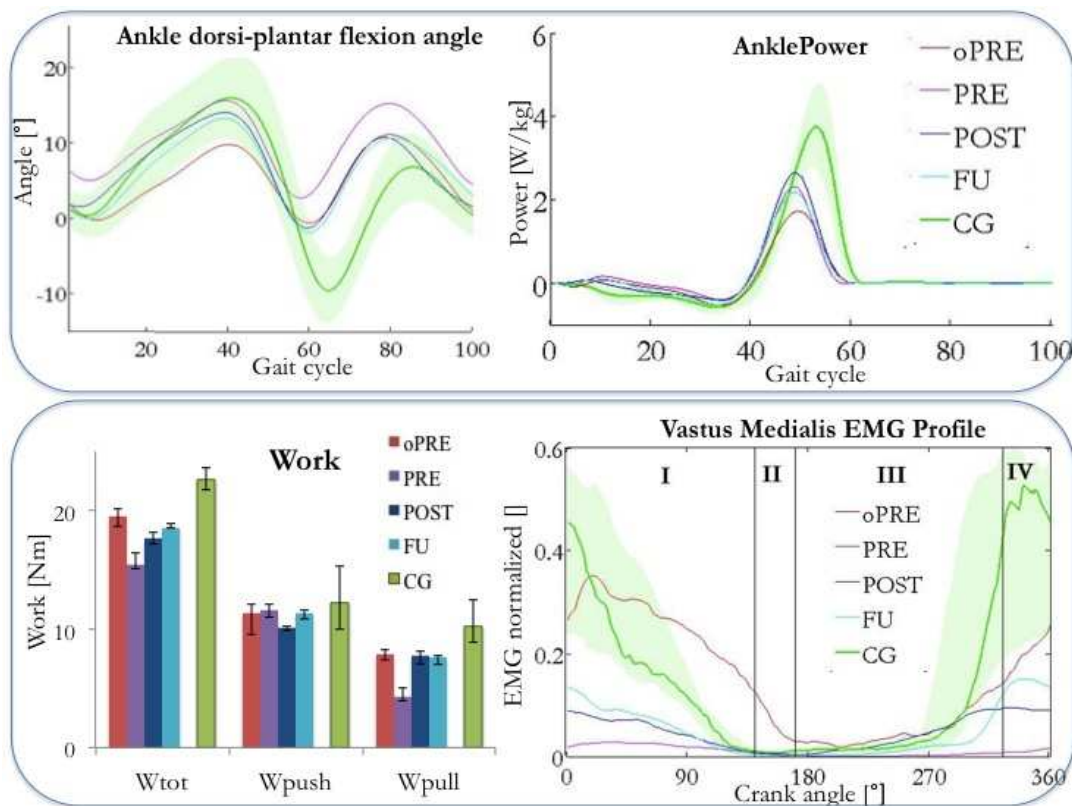


Figura 1: Risultati principali ottenuti da S4 per la gamba paretica. Il pannello superiore mostra i risultati più rilevanti dell'analisi del cammino nel tempo (oPRE, PRE, POST e FU) in confronto con i range di normalità (CG). Il pannello inferiore rappresenta i dati acquisiti durante il test della pedalata e in particolare mostra il trend del lavoro meccanico (mediana e range interquartili) e un esempio del profilo EMG di un muscolo (vasto mediale).

asimmetrie evidenziate dal Symmetry Index (SI) non sono cambiate nel tempo.

L'analisi della cinematica ha mostrato qualche deviazione rilevante a livello distale. In particolare l'angolo di dorsi-plantar flessione della caviglia presentava durante oPRE e PRE un ridotto range of motion (ROM) sia per la gamba paretica che per la sana. Inoltre qualche deviazione era evidenziabile riguardo all'angolo di contatto iniziare (IC) e di minima dorsiflessione. A seguito del trattamento solamente un soggetto (S1) ha ottenuto un miglioramento significativo nella direzione dei range di normalità, mantenuto in FU. A livello della caviglia è stata osservata per tutti i pazienti anche una ridotta potenza propulsiva. Per due di essi, S1 ed S4 (pannello superiore in Fig. 1) è migliorata significativamente (incremento percentuale di 25% e 18% rispettivamente) dopo il training, ma non è stata mantenuta in FU.

Infine la forza scambiata con il terreno rivela alcuni lievi miglioramenti in un paziente (S1) sia nella fase di sopportazione del carico che di spinta.

Il test della pedalata ha mostrato che tutti i pazienti erano in grado di mantenere autonomamente la velocità richiesta durante il test. L'arto sano di uno dei soggetti (S1) ha prodotto un lavoro in pedalata compreso nei range del gruppo di controllo mentre per gli altri tre pazienti (S2, S3 e S4) l'esercizio ha richiesto un valore leggermente superiore. In particolare per S2, S3 ed S4 si sono ottenuti valori eccessivi di  $W_{PULL}$ , indicando una possibile strategia di compensazione del lavoro in spinta  $W_{PUSH}$  della gamba paretica, che infatti presentava valori leggermente inferiori alla normalità (pannello inferiore Fig. 1). A seguito del trattamento non sono stati evidenziati cambiamenti sostanziali nella gamba sana dei soggetti mentre l'arto paretico di 2 pazienti (S2 e S3) è migliorato significativamente grazie ad un maggiore  $W_{PULL}$ , sia in POST che in FU. Analizzando l'Unbalance è stato possibile osservare uno sbilanciamento superiore ai range di normalità per tre pazienti (S2, S3 e S4). Un miglioramento significativo a seguito del trattamento è stato ottenuto per un solo soggetto (S3).

Il segnale elettromiografico dei cinque muscoli (retto femorale RF, vasto mediale VM, bicipite femorale BF, tibiale anteriore TA e gastrocnemio mediale GM) per ciascuna gamba è stato normalizzato tramite il valore di MVC per tutti i soggetti del gruppo di controllo e per due dei pazienti (S3 e S4) mentre gli altri due non sono stati in grado di ottenere valori di massima contrazione opportuni, pertanto i dati sono stati normalizzati rispetto al massimo.

I risultati del gruppo di controllo hanno evidenziato che BF, TA e GM mantengono livelli di attivazione molto bassi rispetto all'MVC (8%, 14% e 15% rispettivamente) e, specialmente gli ultimi due, con una grande variabilità. Analoghi livelli di attivazione e variabilità sono stati osservati per tutti i pazienti ottenendo risultati non utilizzabili nella valutazione della loro prestazione motoria. È importante sottolineare che, poichè il training è stato portato a termine su un ciclo-ergometro con AFO ai pedali, non è stata richiesta attivazione specifica dei muscoli distali e pertanto sono stati ottenuti profili EMG non ripetibili e con basso livello di attivazione.

Qualche risultato più rilevante è stato osservato a livello prossimale (RF, VM e BF). In particolare i profili relativi all'arto sano presentavano risultati generalmente simili dalla

normalità mentre riguardo all'arto paretico sono state evidenziate in tutti i soggetti alcune lievi differenze rispetto al gruppo di controllo nelle tempistiche di attivazione muscolare ottenute durante oPRE e PRE. Un soggetto (S1) è migliorato leggermente nella sessione POST ma non ha mantenuto i risultati in FU, un altro soggetto non è variato sostanzialmente dopo il trattamento mentre gli altri due pazienti (S2 e S4) non hanno mostrato chiaramente un trend di miglioramento nel tempo.

Per quanto riguarda i livelli di attivazione dei due soggetti S3 ed S4, si osserva una diminuzione dell'attivazione del quadricipite a seguito del trattamento, consistente con la diminuita produzione di lavoro durante la fase di spinta  $W_{PUSH}$  commentata precedentemente.

Infine lo studio della co-contrazione di RF e BF permette di osservare che i due muscoli erano correttamente sincronizzati già durante oPRE e PRE per due dei pazienti (S1 e S4). Differentemente S2 durante il test PRE ha ottenuto valori superiori al gruppo di controllo, correttamente modificati sia in POST che FU. In ultimo S3 presenta valori superiori ai soggetti sani, che però vengono mantenuti nel tempo tranne per il FU.

### **Conclusione e sviluppi futuri**

Lo studio di fattibilità di un trattamento di pedalata volontaria aumentato da SEF su giovani soggetti emiparetici ha permesso di verificare che tutti i pazienti hanno correttamente risposto alla stimolazione, tollerando il trattamento. Due dei pazienti hanno lasciato lo studio a causa dell'impegno eccessivo richiesto dal trattamento.

I risultati ottenuti durante le prove cliniche hanno mostrato che tutti i pazienti reclutati presentavano una lieve disabilità in partenza e nel tempo non ci sono state significative variazioni.

Qualche miglioramento distale è stato mostrato nell'analisi del cammino, in particolare riguardo al ROM e alla potenza in spinta della caviglia.

Il test della pedalata ha evidenziato che tutti i soggetti erano in grado di portare a termine autonomamente un esercizio di pedalata già durante le sessioni oPRE e PRE. Inoltre il timing di attivazione muscolare non è cambiato significativamente nel tempo. Qualche risultato si è osservato per i muscoli prossimali mentre in quelli distali il basso livello di attivazione causato dalla presenza dell'ortosi alla caviglia ha reso questi risultati poco ripetibili e non affidabili.

Il disegno dello studio ha permesso di verificare un'ampia variabilità nei risultati sia del-



l'analisi del cammino che della pedalata tra oPRE e PRE. Sarebbe necessario verificare la ripetibilità intra-sessione di questi test su una popolazione di giovani emiparetici.

Uno degli obiettivi principali del trattamento utilizzato era di massimizzare gli effetti della SEF sulla neuroplasticità pertanto sarebbe interessante in studi futuri affiancare ai test utilizzati una verifica degli effetti di riorganizzazione corticale, per esempio tramite transcranial magnetic stimulation (TMS) o tecniche di imaging.

Inoltre, poichè il training è risultato sicuro e la strumentazione richiesta è economica, potrebbe essere interessante proporre il trattamento in ambiente domestico, minimizzando così l'impegno richiesto ai soggetti e alle loro famiglie.

Lo studio, anche se su pochi soggetti, non ha portato evidenze di miglioramento nel caso di disabilità lieve, pertanto studi futuri potrebbero essere condotti indagando l'efficacia del trattamento di pedalata volontaria aumentata da SEF su bambini e adolescenti con riduzione severa dell'abilità di locomozione, possibilmente incrementando la numerosità del campione analizzato.

**Struttura della tesi**

Il presente lavoro si sviluppa in quattro capitoli. Il primo presenta una descrizione dell'emiparesi e dei problemi ad essa connessi. Segue un'analisi del principio neurofisiologico su cui si basa la stimolazione elettrica e lo studio dello stato dell'arte connesso alla riabilitazione di soggetti emiparetici con SEF. Infine vengono definiti gli obiettivi della tesi.

Il secondo capitolo è dedicato alla descrizione dello studio e dell'intervento pianificato per ciascun soggetto. Inoltre vengono discussi la strumentazione e i metodi utilizzati durante i test di verifica dell'efficacia del trattamento.

Il terzo capitolo presenta una prima parte focalizzata sui pazienti reclutati e sulle caratteristiche del trattamento di SEF per ciascuno di essi. Nella sezione successiva sono discussi i risultati ottenuti dal gruppo di soggetti sani durante il test della pedalata e, a seguire, i dettagli relativi a ciascun paziente singolarmente.

Infine, il quarto capitolo fornisce un quadro generale del lavoro focalizzandosi su possibili sviluppi che potrebbero essere approfonditi durante studi futuri.

## **Summary**

### **State of the art and aim of the work**

The present work is focused on the assessment of the potential benefit volitional cycling treatment augmented by functional electrical stimulation in the rehabilitation of young hemiparetic subjects.

Hemiparesis is a one-side partial loss of motor function caused by a number of different medical conditions mainly related to brain or spinal cord such as stroke, traumatic injury or cerebral palsy. The pathology causes muscular weakness and high spasticity, it affects fine and gross motor functions resulting in unbalance, walking impairments and difficulties to perform every day activities.

Two of the main causes of hemiparesis in young subjects are cerebral palsy and stroke. Cerebral palsy (CP) is a group of motor disorders that appears in early life and is characterized by a non-progressive damage of the developing brain. The main risk factors of CP are the premature and low-weight birth. Some recent studies have assessed that the incidence of this pathology is increasing in the developed world as the infant mortality rate is significantly decreasing. The hemiplegia interests the 20-30% of CP population while the majority of the subjects presents diplegic CP.

Stroke disease results in a loss of neurological function due to disturbance in blood flow in brain vessels creating a hypo-oxygenation that creates neuronal damage.

Neuromuscular electrical stimulation is becoming a conventional method to improve motor recovery in people affected by neurological disorders as it reduces the recovery time of patients and some evidences support that its benefits are maintained over time. In particular, functional electrical stimulation (FES) has been widely applied because it is oriented to the restoration of functional movements. The neurophysiological principle is based on the generation of action potential in the lower motor neurons by delivering low level of electrical voltage or current to sensory-motor fibers. This electrical pulses elicit the nerves toward the activation threshold causing a contraction of the muscles controlled by the motor unit.

The effectiveness of FES in hemiparesis rehabilitation is supported by a number of studies [1], [2], [3]. In particular muscular strength and atrophy as well as venous return and cardiovascular fitness can be significantly improved. Moreover, the reorganization of voluntary movement and recovery of function during movement are shown.

The neuroplasticity is supported by FES treatments as they provide the patients with a sensory volley that, ascending through the spinal cord till reaching the brain, can increase the activity in the spinal and cortical circuits [4]. This effect is particularly relevant if combined with voluntary effort.

Moreover some studies [5] observed a greater flexibility of the central nervous system of young subjects, thus obtaining a wider recovery of motor function in patients who were damaged in the early life.

Further effect on neuroplasticity can be achieved performing repetitive and goal-oriented task. A safe, economic and widely accessible possibility to guarantee this approach is provided by FES augmented cycling training. This direction is particularly interesting also to recover the locomotion ability, that is one of the main goal of the neuro-motor lower limb rehabilitation. In fact the kinematic pattern of walking is very similar to the one of cycling: both are cyclical, require reciprocal flexion and extension movement and have alternating muscle activation of agonist/antagonist muscles in a well-timed and coordinated manner.

The instrumentation needed for FES cycling treatment includes a motorized cycle-ergometer and a stimulator that provides the electrical stimuli through surface electrodes positioned over the target muscles. In particular stimulation is usually delivered to knee flexors and extensors (quadriceps and hamstring), to hip extensors (gluteus maximus) and sometimes to dorsal and plantar flexors (tibialis anterior and triceps surae muscles). One of the most promising stimulation strategy is obtained following the physiological muscular strategy extracted on healthy subjects in a previous study [6].

In recent years the application of FES augmented cycling in the lower limb rehabilitation of hemiparetic adult subjects has been increasingly used, demonstrating the effectiveness in improving motor recovery and walking ability. Anyway, only few studies [7] are focused on FES for children rehabilitation although the encouraging premises. Recently a study of feasibility on five cerebral palsy adolescents has been performed [8] and results give

some evidence that the stimulation was well tolerated. A recent study by Trevisi and colleagues [9] on two hemiparetic children has been carried out. The patients underwent 21 sessions of FES-cycling treatment and some improvement in terms of activation timing, symmetrical cycling and gait strategy was obtained. A randomized study [10] performed on sixty-two hemiparetic children assessed that a standard cycling training (with no FES intervention) does not promote significantly the motor recovery in young hemiparetic subjects. Thus, the augmented proprioception induced by FES could induce wider benefits. The main objective of the present thesis is to assess the feasibility and the effectiveness of FES augmented volitional cycling in improving gait and lower limb motor function on hemiparetic adolescents.

In order to study the motor recovery of the subjects, clinical condition, walking performance and cycling assessment test was carried out. The present work is mainly focused on the acquisition and data analysis of pedaling assessment test and on the evaluation of the whole results for each patient.

### **Material and methods**

Six patients have been recruited from the Neurological Institute “Carlo Besta” in Milan. Inclusion criteria were: age between 10 and 18 years, diagnosis of acquired hemiparesis, possibility of autonomous walk, low spasticity level in the lower limb (Modified Ashworth Score < 2), lack of articular limitation, lack of pharmacological treatment with botulinum toxin or of surgery. No other rehabilitation programs were allowed during the study. Moreover, the subjects were excluded if electrode allergy or intolerance to stimulation was found. All patients received an information sheet and family compliance was required. The medical ethics committee of Institute Besta approved the research protocol.

All participants were trained 3 times a week, receiving a total of 21 sessions lasting 30 minutes each. Each session consisted of 5 minutes of passive pedaling on a motorized cycle-ergometer (warm-up phase), 20 minutes of FES synchronized with voluntary pedaling and 5 minutes of passive pedaling (warm-down phase). FES was delivered to gluteus maximus, quadriceps, hamstring and tibialis anterior of both legs following a physiological muscular strategy extracted on healthy subjects in a previous study [6]. The RehaStim stimulator (Hasomed GmbH) together with the MOTOMed Viva2 ergometer (Reck GmbH) were used for the intervention.

To assess the effectiveness of the treatment, the subjects were tested in four different sessions, two before the treatment and two after. Before the treatment the tests were performed at a distance of 7 weeks during which the subjects were supposed to perform their daily activities. The two assessment sessions, oPRE (observation PRE) and PRE in the following, allowed to monitor the trend of neuromotor variation due to the physiological growth, particularly marked during the considered range of age.

The assessment tests after the treatment (POST and FU in the following) were performed in order to evaluate both short-term and long-term effect of the FES-cycling trial. In fact the POST test was performed immediately after the end of the treatment while the follow-up (FU) session was carried out 12 weeks after the end of the intervention; during this period the subjects came back to their daily life activities without any particular treatment.

Each assessment session was composed by three different tests: the clinical assessment, the gait analysis and the pedaling test.

The clinical assessment was performed at “Carlo Besta” Neurological Institute Foundation and consisted of the evaluation of some clinical scales. The first one was the Winter scale, intended to investigate the functional deficit level during walking of CP subjects. Another evaluation concerning the locomotion ability was the Observational Gait Scale (OGS) that was obtained from a video recorded during walking. The Gross Motor Function Measurement (GMFM) was used to study the gross motor skills and was developed for children and adolescents with CP. The Boyd test assessed the distal selective motor voluntary control during a dorsi-plantar flexion exercise. At last the Modified Ashworth scale evaluated muscular spasticity.

The gait analysis is a standardized technique of movement analysis that provides quantitative information on the locomotion ability. It was performed at “Luigi Divieti” posture and movement analysis Laboratory with an optoelectronic system ELITE 2000 (BTS Company SpA, 8 cameras, 100 Hz) integrated with two force platform. The optoelectronic system recorded the position of markers positioned on the subjects following the Davis protocol. The outcome measures extracted from this test concerned the spatio-temporal parameters (mean velocity, step length of paretic and healthy leg  $L_{PL}$ ,  $L_{HL}$  and Symmetry Index  $SI$  computed as the ratio between  $L_{PL}$  and  $L_{HL}$ ), kinematics (angular values of ankle, knee

and hip on frontal, sagittal and horizontal plane), kinetics (moment and power produced at ankle knee and hip on sagittal plane) and vertical forces exchanged to the ground.

The last assessment test was aimed at studying the performance during voluntary pedaling as it was the motor task that was directly trained during FES treatment. This test was performed at NeuroEngineering And medical Robotic Laboratory (NEARLab) and consisted of 1 minute of passive cycling, followed by 2 minutes of voluntary pedaling during which the subjects were asked to maintain a constant speed of 30 rpm. A motorized cycle-ergometer (Thera-Live<sup>TM</sup>, Medica Medizintechnik GmbH, Germany) customized with resistance strain gauges mounted at the crank arms was used to measure the torque generated by each leg during pedaling. The crank angle, the cadence and the torque signals were acquired at a frequency of 200 Hz with a PC running Linux Real Time. During the pedaling test, EMG signals of the rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA) and gastrocnemius medialis (GM) of both legs were also measured. A multi-channel signal amplifier working at 1 kHz (Porti32TM TMSi, Netherlands) was used. Bipolar surface electrodes were placed over the intended muscles as SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) recommends in order to minimize the possibility of cross talk between muscles. Within each session an isometric Maximum Voluntary Contraction (MVC) test was also performed. This test was intended to provide information on the maximal muscular activation level of each level thus representing a reference level to compare the amount of activation between different sessions. However it is important to highlight that it is not always guaranteed that the reference EMG values recorded during MVC represent the maximal neural drive during pedaling.

The outcome measures extracted from the pedaling test were the cadence maintained by the subject during the voluntary pedaling, the mechanical work produced by each leg, the unbalance between them and the muscular activation timing.

The active torque profiles during voluntary pedaling were estimated by subtracting the passive torques from the measured total torques. The work produced by each side was computed as the integral of the active torque profiles mapped as function of the crank angle. The median work values produced by the paretic ( $W_{PL}$ ) and the healthy ( $W_{HL}$ ) legs were calculated on all the single-revolution values. Moreover, the unbalance (U) in

the work between the paretic and healthy leg was computed as  $U = \frac{|W_{HL}-W_{PL}|}{W_{HL}+W_{PL}}\%$ . Its value ranged from 0% (identical works) to 100% (paretic work =0). The work values were also analysed dividing the contribution during pulling and pushing phases of each cycle ( $W_{PULL}$   $W_{PUSH}$  respectively).

Muscle activation timing and co-contraction of rectus femoris and biceps femoris muscles during cycling was extracted from electromyographic signals. After a standard EMG analysis (high-pass filter at 10 Hz, rectification, low-pass filter at 5 Hz), the activation timing of each muscle was computed as follows:

1. A spline function was used to define the EMG envelope as a function of the crank angle. The revolutions that differ from mean profile of more that 3 standard deviation were considered outlier and removed.
2. The remained profiles obtained in 20 second of acquisition were averaged. Please note that in 2 minutes of acquisition 6 mean profiles should be obtained.
3. Each of the 6 mean profiles were normalized with two different methods. The MVC values were used only for the subjects that during all the pedaling sessions were able to achieve, for each muscles, MVC values above the activation level obtained during pedaling. Otherwise the maximum activation value obtained during the pedaling was used for normalization. Please note that in the first case a comparison of the muscular activation level between sessions was possible.

The co-contraction between the rectus femoris and the biceps femoris was evaluated using a co-contraction index (CCI) defined in a previous study [9]. The CCI of the j-th mean profile was computed as  $CCI(j) = \frac{S_{Overlap}(j)}{S_{RF}(j) + S_{BF}(j)}$  where  $S_{RF}$  and  $S_{BF}$  denote the surface area under each normalized EMG profile of RF e BF, respectively.  $S_{Overlap}$  is the overlap area of the two EMG profiles.

Normality ranges for the outcome measures related to the pedaling test were computed on an age-matched control group (CG) of 6 healthy volunteers (age  $14.3 \pm 1.0$  years).

A statistical analysis considering each subject individually was also performed. A Kruskal-Wallis test was used to compare outcome measures of both gait analysis and pedaling test obtained at the different time points. If a significant difference between oPRE, PRE,



POST and FU assessments was found ( $p < 0.05$ ), a post-hoc analysis was performed comparing pairs of tests. A Mann-Whitney U test was also performed for the pedaling test to compare each patient with the control group at the different time points. No statistical analysis comparing the four subjects was performed because of the low sample size.

## Results

Six hemiparetic subjects have been recruited from the Developmental Neurology Unit of Besta Institute but two of them withdrew with the study during the second week of the FES treatment as the effort required by the training was not compatible with their every day activities. Thus the training was concluded by four male patients of age between 12 and 17 years with diagnosis of acquired hemiparesis. Three subjects were affected by cerebral palsy while the last one experienced a stroke 8 years before the beginning of the study.

The clinical tests showed that all patients were slightly impaired at baseline. In fact all the scores obtained are just below the normality ranges but the spasticity level that was moderate for the CP patients and severe for the stroke subject. After the treatment the clinical scales maintained the values obtained at baseline.

An example of the main results obtained during gait analysis and pedaling test by one of the subjects (S4) is shown in Fig. 2.

The gait analysis allowed to observe that the subjects were able to walk at a speed just below the ranges of healthy subjects already at baseline. According to a previous study [11], the speed value obtained by all subjects was characteristic of people with lack of substantial limitation. The step length of the paretic and healthy leg showed few deviation already during oPRE and PRE tests, maintained after the training. For all the subjects the values of symmetry was within the normality ranges.

The kinematics showed that during oPRE and PRE tests some deviation occurred at distal level. In particular the angle of dorsi-plantar flexion of the ankle was characterized by reduced range of motion for both paretic and healthy leg for all the subjects. Angles of initial contact and minimum dorsiflexion were also impaired. After the treatment one of the subjects (S1) obtained significant difference in his ankle dorsi-plantarflexion angle towards the normality ranges.

Other results at ankle level were obtained from the kinetics that highlighted a reduced

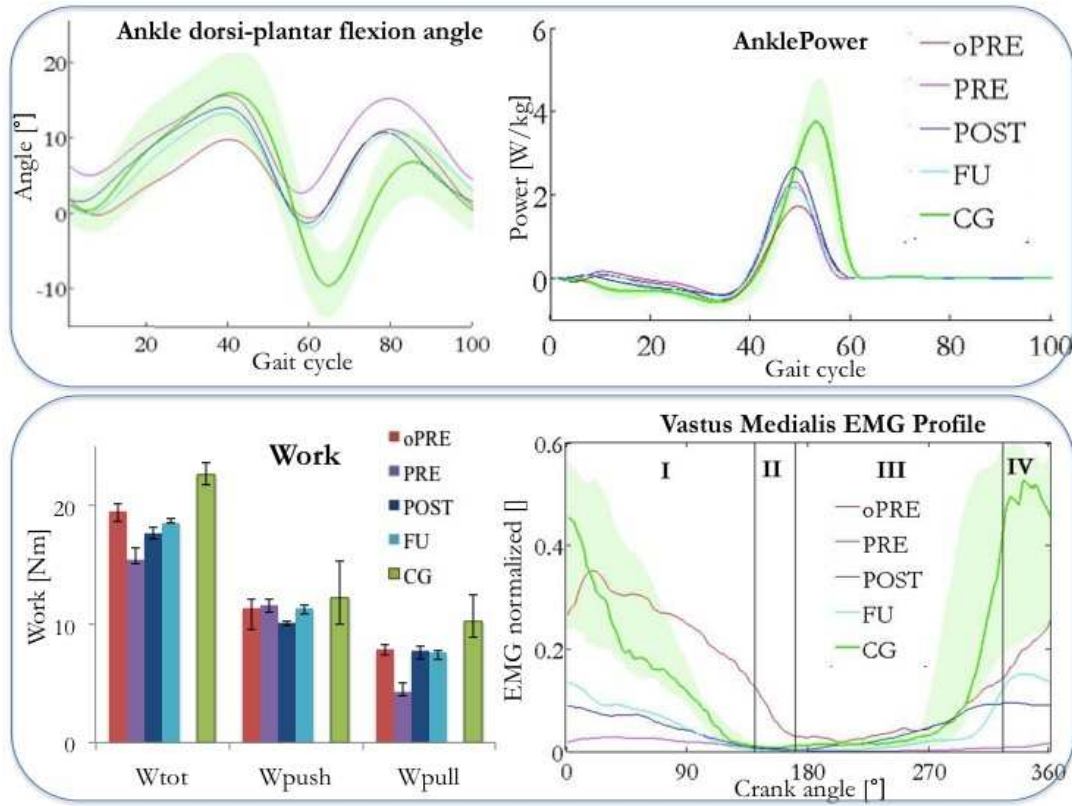


Figure 2: Main results obtained for paretic limb of S4. The upper panel shows the most relevant gait analysis results over time (oPRE, PRE, POST and FU) with respect to the normality ranges (CG). The lower panel represents the trend of the work as median and inter-quartile ranges (error bars) as well as an example of the vastus medialis profiles over time acquired during the pedaling test.

propelling ankle power that was significantly improved after the training for two out of four patients (relative increase of about 25% for S1 and 18% for S4, see Fig. 2).

In terms of vertical forces exchanged to the ground, some improvements both in loading response peak and push-off peak were obtained for one out of four patients (S1).

The pedaling assessment showed that all the patients were able to maintain autonomously the speed required during the test. The work produced by the healthy leg during cycling was perfectly within the control group range for S1 while it was above the normality ranges for S2, S3 and S4 (see Fig. 2). In particular an exaggerated pulling work was produced, partially sustaining the pushing phase of the paretic limb, that in fact presented reduced values. No changes occurred after treatment for the healthy leg while the paretic limb was significantly improved for two of the subjects (S2 and S3). The results were maintained

at FU.

The unbalance between the overall work produced by the two legs assessed the symmetry of the movement. Three out of four subjects (S2, S3 and S4) obtained less symmetrical movement than the control group. A significant improvement of the symmetry was observed for one of these patients (S3) after the treatment.

The muscular activation timing during pedaling was also assessed. The EMG profiles of S1 and S2 were normalized to the maximum activation obtained for each muscles during pedaling as they were not able to perform the MVC test obtaining results over the activation reached by each muscle during the pedaling exercise.

Differently for all the six healthy subjects that composed the control group the MVC normalization could be used. Their data assessed that BF, TA and GM had a very low activation level (peak value at 8%, 14% and 15% respectively) and, especially for TA and GM, a high variability was observed. These results can be explained as the pedaling test was performed on a cycle ergometer that fixed the ankle angle at  $90^\circ$ . The high variability level was observed also for all the patients thus obtaining results not useful for the evaluation of their motor performance. However, it is important to highlight that, since the training was performed on a cycle-ergometer with AFO, no specific activation of distal muscles was required, resulting in a low amplitude and not repeatable EMG profiles.

The activation timing of proximal muscles (RF, VM and BF) of the healthy leg did not show significant deviation thus no compensation strategy occurred. Concerning the paretic limb, one of the subjects (S1) had deviations that was slightly improved in the POST session but not maintained at FU. S2 did not change over time while for the other two subjects (S3 and S4) some variation were observed but no improvement trend could be clearly observed. The activation level obtained on the two subjects that correctly performed the MVC showed that the relative activation level of proximal muscles after the treatment was decreased.

Finally, the study of the co-contraction of RF and BF showed that these two muscles were correctly timed already at baseline for two patients (S1 and S4). S2 during PRE test obtained an higher value that after the treatment was correctly restored both at POST and FU. At last S3 showed higher value, maintained over time but for FU assessment.

## **Conclusion and future developments**

The feasibility of an FES augmented voluntary cycling treatment on young hemiparetic subjects was assessed: all the recruited patients responded to stimulation and well tolerated the treatment.

The results obtained during the clinical assessment tests showed that all the recruited subjects were slightly impaired at baseline and no variation occurred over time.

Some distal improvement in locomotion ability was observed concerning the range of motion and the propelling power of the ankle during the gait analysis. The pedaling test highlighted that the subjects were able to perform the pedaling exercise with only few deviation in the production of work already at baseline. Moreover the muscular activation timing did not significantly changed over time. Some more results were obtained for proximal muscles while no clear improvement was observed in distal muscles (TA and GM).

The study design pointed out that high variability between the oPRE and PRE sessions occurred. In fact some results significantly changed between the two sessions both on gait analysis and pedaling test. In the future, researches should investigate the intra-session repeatability of these tests on young hemiparetic subjects.

One of the main aim of the FES augmented volitional cycling was to maximize the effect of the electrical stimulation on the neuroplasticity, thus future study could also investigate the cortical reorganization occurred after the treatment.

Since the training was safe and the instrumentation was quite low-priced, the treatment could be delivered in a domestic setting thus minimizing the effort for both young patients and their family. Further investigation are required to assess this possibility.

The present study, although on a small sample size, did not obtain evidence of motor recovery on slightly impaired population. Further studies could be performed in the future assessing the effectiveness of FES augmented voluntary pedaling on subjects with more severely impaired locomotion ability. Moreover a bigger sample size would be required to validate the results of the study.

**Structure of the thesis**

The present work is organized in 4 chapter. The first one give an overview about the hemiparesis disease and the neurophysiological principle of FES. Moreover the state of the art on FES-cycling treatment is studied and the aim of the thesis are detailed.

In the second chapter the study design and the intervention planned for each subject are presented. Moreover the instrumentation and the methods used during the assessment tests, especially concerning the pedaling test, are widely discussed.

Chapter 3 reports details on the recruited patients at baseline and on the treatment performed by each on them. The following sections present and discuss the results obtained during the assessment tests. In particular the first part shows the data concerning a group of healthy subjects recruited as control group for the pedaling test. Then, as the study is a case series, the results of each subject are presented singularly.

Finally, Chapter 4 provides a last overview on the project concluding with limitation and future developments that could be explored in future works.

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# Chapter 1

## Introduction

### 1.1 Hemiparesis in young subjects

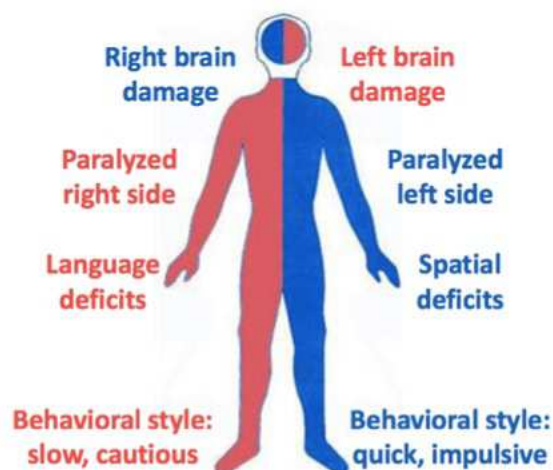
Hemiparesis is a one-side partial loss of motor function caused by a number of medical conditions, mainly related to brain or spinal cord [17], such as stroke, traumatic brain injury or cerebral palsy (CP).

Hemiparesis can be congenital or acquired. In the first case the disease already exists at birth or it occurs during the first period of life. In the second case the pathology appears after the age of 3 years. In both cases the pathology, after the acute phase, becomes chronic.

The hemiparesis is usually caused by cerebral damage that entails weakness in the contralateral side of the body (see Fig. 1.1).

Depending on the causes of hemiparesis, different physiological functions can be affected. Behavioural disparity and difficulty linked to speech or memory as well as a loss of motor control can be observed. In particular the maintenance of symmetry is critical due to the weakness of the muscles involved in the movement of the arms, the legs and sometimes the face of the affected side.

Together with the muscle weakness, individuals with hemiparesis present abnormally high muscle spasticity in the affected extremities, which result in fine and gross motor developmental delays. Poor selective muscle control often causes coactivation of agonist and antagonist muscle groups. Spasticity and abnormal tone that is present in the muscles

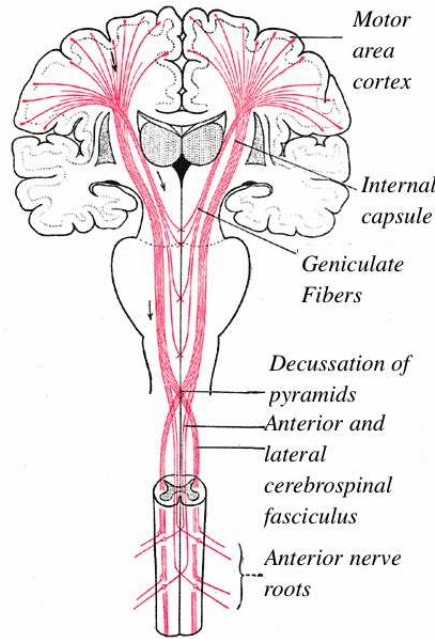


*Figure 1.1: Schematic representation of hemiparesis disease. If left brain damage occurs, right limb and language area are interested, while right damage affects left side muscles and leads to spatial deficit.*

of the affected subjects can cause abnormal forces at the joints, which can lead to bone deformity, joint instability, and muscle contractures. The balance impairments due to muscular weakness and poor selective motor control may lead to diminished independence and a lack of physical activity such as locomotion [8].

In order to have a better understanding of the damage that generates hemiparesis, an analysis of the motor pathway is provided (see Fig. 1.2). Motor impulses originate in the motor area of the cerebral cortex and, more in particular, in the upper motor neurones of the corticospinal tract. The axons of these cells pass deeply in the cerebral cortex through the internal capsule and descend towards the midbrain and the medulla oblongata. In the medulla oblongata 80% of the fibers pass to the opposite side (100% if only the fibers that project to the limb are considered) and descend in the white matter of the lateral funiculus of the spinal cord. The remaining 20% proceed on the same side forming the anterior cerebrospinal fasciculus. At different levels of the grey matter of the spinal cord the axons have synapses with the lower motor neuron that bring the information to the various body districts. [18].

Brain tissue damage occurs at different levels. For example stroke is prevalently localized in the irrigation of the middle cerebral artery, e.g. internal capsule. In this site the fibers are bundled together and so even a slight stroke can provoke a significant loss of motor



*Figure 1.2: Schematic representation of motor pathway in a healthy subject.*

control.

The World Health Organization (WHO) estimates that approximately 5 million people remain permanently disabled after stroke, causing serious medical, socio-economic and rehabilitation problems with increasing age of population [19]. As the 88% of the individuals that experienced stroke are consequently affected by hemiparesis, stroke is reported as one of the major causes of hemiparesis.

The incidence of hemiparesis disease in a young population is less relevant than adult population but some studies resulted in an increased awareness of the frequencies and features of stroke syndromes in children [20].

Epidemiology, etiology and taxonomy of two of the main causes of hemiparesis in young subjects are better described in the following.

**Stroke disease** A stroke results in a loss of neurological function due to disturbance in the blood flow in brain vessels. The etiology divides the stroke into two main categories: the ischemic stroke is more frequent and is caused by a blockage of the blood flow caused by thrombosis or embolism. Hemorrhagic stroke occurs due to rupture of the vessel wall. Both the conditions produce hypo-oxygenation that creates neuronal damage.

Although stroke is a pathology that typically arises in elderly people, childhood stroke is emerging as a serious and frequent disorder. In contrast to adult stroke, the study of the etiology and risk factor of childhood stroke is in a very early stage of research development with no randomized controlled trials [20].

It has been calculated that the international incidence ranges from 1.3 to 13 per 100,000 live-born children and the cost of pediatric stroke hospitalization in US is more than \$42 million per year [21]. Considering ischemic stroke, a study in the US [22] revealed that after the acute phase of the disease, 35% of children were neurologically normal, 55% developed cognitive or motor problems, and 10% had died by the outcome evaluation period. The same study on hemorrhagic children revealed that 38% of children were neurologically normal, 41% had cognitive or motor abnormalities, and 20% had died by the outcome evaluation period. Moreover, more than one third of the children that experimented a stroke has a recurrent stroke in the following years.

**Cerebral palsy disease** Cerebral Palsy (CP) is a group of motor disorders that appears in early life and is characterized by a non-progressive damage of the developing brain resulting in impaired motor functions due to abnormal control of the central nervous system over skeletal musculature [23].

For many years CP had been ascribed to birth trauma but recent advances in neonatal management have not shown a decline in the incidence of CP. On the contrary, with the decline in infant mortality rate, there has been an increase in the incidence and severity of CP. In fact the most important risk factors seem to be the prematurity and low birth weight [24]. The incidence of this pathology in the western world is of 2-2.5 every 1000 live-born children (in Italy data reported 2 out of every 1000 live-born children) [25].

CP has a very complex and multifactorial etiology. The main causes are genetic, anoxic (maybe caused by perinatal stroke), inflammatory, infectious, traumatic and metabolic.

Generally a taxonomy based on the interested parts of the body is provided [24]:

- **Quadriplegic CP:** interests the 10-20% of population and is the most severe form of the pathology, involving all the four limbs. Voluntary movements are few and intellectual impairment is severe.

- Hemiplegic CP: interests the 20-30% of the CP population. It is an unilateral paresis that affects mainly hand and upper limb functions (flexion of elbow and wrist) as well as ankle dorsiflexion and aversion of the foot. Sensory abnormalities in the affected limbs are common.
- Diplegic CP: interests the majority of the CP population. Lower limb are more severely involved, especially in the dorsiflexion of the ankle and in the flexion of the hip and the knee.

Moreover, on the base of the type of neuromuscular deficit, CP can be classified into spastic (the majority of case, counting for 70-75%), dyskinetic (10-15%) and the rarer ataxic, hypotonic and mixed CP. Spastic CP patients exhibit piramidal involvement with weakness, hypertonia, hyperreflexia and clonus. Dyskinesia is characterized by an extrapiramidal involvement that results in rigidity, chorea and dystonic movement.

## 1.2 Functional electrical stimulation

### 1.2.1 Historical overview

The first scientific evidence that electrical current can activate muscles was provided by Luigi Galvani during his studies on bioelectricity in the late 18th century [26]. During the following two centuries various studies documented the interest in electrically induced muscular movements.

The first real effort to apply electrical stimulation as a method for recovering motor function in disabled people was made by Liberson and his colleagues [27] in 1961, when the technology gave the possibility to built miniaturised, battery powered, portable electrical stimulators. They started to use a portable stimulator to compensate for the drop foot in hemiplegic patients.

Since then, a number of different works have been undertaken, in particular thanks to Loize Vodovnik who worked towards reproducing functional movements using electrical stimulation in neuromotor rehabilitation.

Vodovnik himself introduced the definition of Functional Electrical Stimulation (FES) as “the stimulation causing muscle contraction, without neural control, in order to obtain a

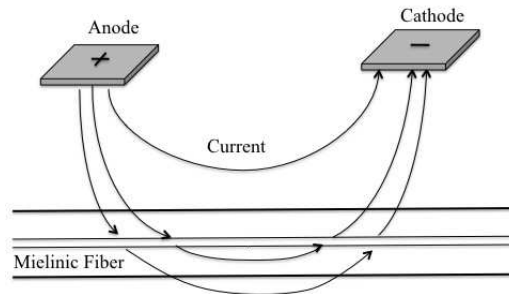
useful and functional movement” [28].

An FES system can be defined as a “functional neuroprosthesis” because it substitutes the impaired link between the central nervous system and the musculo-skeletal system in order to re-activate muscles and nerves below the lesion, thus producing functional movement. Electrical stimulation is applied mainly on subjects with lesions that preserve the peripheral nervous system intact. Included in this condition are patients with cerebral palsy, multiple sclerosis or people whose muscles are paretic or plegic due to cerebro-vascular stroke.

Today FES has broad clinical applications: as orthosis, the subjects wear a device to restore functional movement such as standing or walking. Moreover, from a rehabilitative point of view, the aim is to modify an existing condition so that a carry over of the benefit of the treatment results from temporary stimulation. This persistent effect is probably caused by a cortical reorganization, as will be discussed in what follows.

### 1.2.2 The neurophysiological principle

Electrical stimulation is based on the generation of action potential in lower motor neurons by delivering low level electrical voltage or current to sensory-motor fibers (Fig. 1.3).



*Figure 1.3: NEurophysiological principle of FES. The anode sends a positive charge to the cellular membrane which is hyperpolarized under the positive electrode. The positive charge, attracted to the cathode, leaves the membrane thus depolarizing the area under the negative electrode. If depolarization is over the threshold, action potential is generated.*

When a current flows through the volume beneath an anode and a cathode, it raises the cellular membrane potential of nerves and muscle toward the activation threshold. Since the nerves are usually more superficial than the muscle fibers and, moreover, the activation

threshold needed for eliciting a nerve fiber action potential is 100 to 1000 times less than the threshold for muscle fiber stimulation [29], the effect of electrical stimulus is to excite more the nervous fibers rather than the muscular fibers. Thus the innervated muscles can be more easily stimulated with the effect of generating an artificial muscle contraction with the same dynamic as the natural contraction (muscular depolarization due to activation of the motoneuron).

Stimulation can be applied in monopolar or bipolar configuration depending on the placement of the electrodes. In the following, a bipolar configuration will be considered. The electrical stimulator is designed to regulate either current or voltage. Current-controlled stimulators are usually preferred because they allow a direct control of the current. Thus the risk of damage caused by injection of a high current level due to a decrease of impedance of electrode-skin interface is avoided. Current stimulus waveform can either be monophasic or biphasic, as shown in Fig. 1.4.

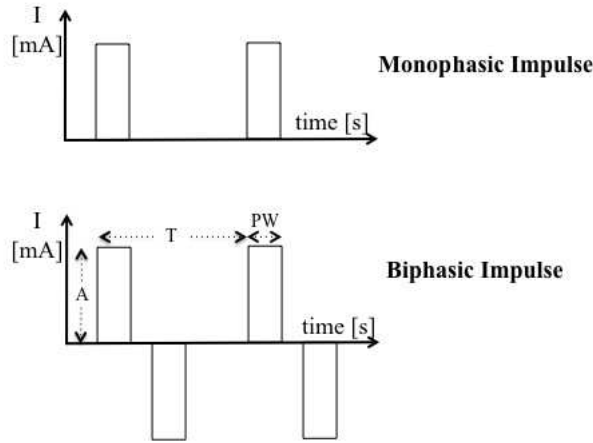


Figure 1.4: Current stimulus waveform.  $A$ : stimulus amplitude,  $PW$ : pulse width,  $T$ : period, i.e. inverse of the stimulation frequency

The biphasic configuration is usually preferred as it balances the charge injected in the muscle. In fact, since the product between  $A$  and  $PW$  represents the injected charge, the biphasic stimulus is characterized by a null net charge, preserving galvanic process that can cause tissue damage [30].

Stimulation can be modulated varying some parameters:



- current amplitude (A): define the amplitude of the stimulus. A threshold of amplitude beneath which the action potential is not generated can be defined. The typical values differs significantly from the electrodes configuration (see above).
- pulse width (PW): together with A is used to set the injected charge. Typical values are between 0.1 and 0.5 ms.
- stimulus frequency ( $1/T$ ): contribute to the regulation of the muscle fatigue and force of the mechanical. Typical values are between 20 and 30 Hz.

The electrical stimulation can be provided through different kind of electrodes depending on the application (Fig. 1.5) [31].

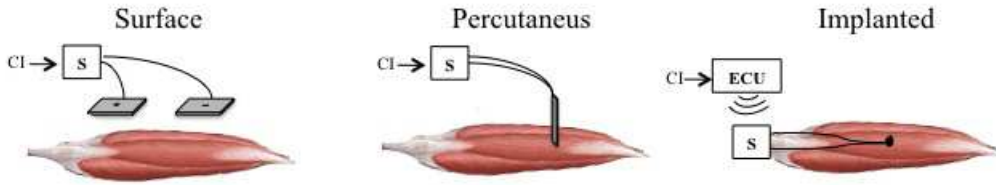


Figure 1.5: Configuration of bipolar electrical stimulation system with surface, percutaneous or implanted electrodes. CI: Control Input, S: Stimulator, ECU: External Control Unit.

Being not invasive and easy to use, the surface electrodes are the most commonly used in clinical rehabilitation. They are directly attached to the skin surface over the target muscle. Typical current amplitude values are from 10 to 130 mA. The major disadvantages include lack of selectivity in muscle activation and inability to stimulate muscles whose nerves are positioned deeper in the volume. The percutaneous system use intramuscular electrodes inserted through the skin in the muscular tissue that remain in place for a certain time period. The stimulation equipment is placed externally and provide current with amplitude usually lower than 25 mA. The selectivity provided in this configuration is good but the insertion site can be subject to infections. This kind of system is used for a short term application because otherwise the electrodes needs to be periodically replaced. The third configuration is the implantable system that needs an invasive surgery for the permanent placement of the electrodes. The stimulator is also implanted and is controlled from a device generally external with a transcutaneous transmission of information and energy.

Typical current values in implanted configuration ranges from few mA to 15 mA [32].

Thus, although both percutaneous and implanted electrodes offers more precise stimulation of the target muscles, the surface electrodes configuration is a valid, non invasive method for the electrically-inducing muscle contraction in clinical settings.

The execution and control of a coordinated and “functional” movement is very complex involving the synergy between many muscles (at least two, the agonist and the antagonist).

The muscle is composed by a number of muscular fibers. Each fiber is controlled by a motoneuron but each motoneuron can activate several fibers. The motoneuron, its axon and the muscular fibers that it innervates are defined Motor Unit (MU). Muscle force is modulated from the Central Nervous System (CNS) through two mechanisms, the temporal and the spatial summation. The first one involves the increase of the fire rate of the single MU, the second one depends on the progressive recruitment of an increasing number of MUs [33]. In fact when a muscle fiber is electrically stimulated it responds with a twitch. If the stimulation is performed by a train of impulses of frequency superior to the inverse of twitch duration, then temporal summation will occur developing a bigger and, above 10 Hz, continuous muscular force (see Fig. 1.6). The duration and the amplitude of each

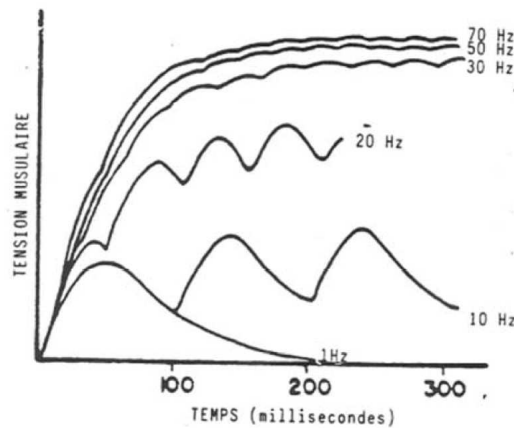


Figure 1.6: Response of muscular force at stimuli. Each curves refers to different stimulation frequencies of motor nerve. For low frequency (1 Hz) the single twitch can be observed. For higher frequency (30 Hz or more) the maximal force is developed reaching the tetanic contraction. At 10 Hz a tetanic fusion can be observed.

twitch profile are different depending of the fiber type that composes the muscle. In fact

skeletal muscles present three kinds of fibers called type I, IIA and IIB. Type I or slow oxidative (SO) fibers are characterized by small cross-sectional area and by a slow and low amplitude twitch response. Thanks to their wide oxygenation, this fibers are more fatigue resistant and recover rapidly. Fibers of type IIA or fast oxidative (FOG) use both the oxidative and the glycolytic metabolism resulting with an intermediate behaviour. The IIB fast glycolytic fibers (FG) present the biggest cross-sectional area and, when stimulated, produce a short, broad twitch. These fibers mainly depend on glycolytic metabolism and so rapidly incur in fatigue.

All fibers in a motor unit have similar contractile and fatigue characteristics and, therefore, motor units are classified on the basis of fibers type. During voluntary muscular contractions the motor units are recruited progressively as function of increasing diameter of the fibers. Consequently during physiological contractions type I fibers activate first (with the smallest diameter but fatigue resistant) followed by type IIA and, finally, by type IIB (biggest diameter, not resistant to fatigue).

On the contrary, during electrical stimulation the recruited order follows two principle: the physical distribution, as the more superficial fibers are recruited with a lower stimulation level, and the fiber diameter. In fact, according to the literature, fiber with bigger diameter (type II) are innervated by bigger axons that have a lower activation threshold [34]. Thus, as shown by Fig. 1.7, the resulting recruited order is different from the physiological one: the first fibers to be activated are the more superficial and, moreover, the one with a larger diameter (type II, more easily fatigued).

Therefore, although the generation of action potential has the same basis for artificial and physiological mechanism, the study of the muscular contraction during electrical stimulation shows some important differences:

- no physiological turn over of the fibers can be highlighted because all motor unit over threshold are simultaneously activated.
- the recruited order is inverted as for low stimuli only larger diameter (the most fatiguable) fiber are activated.
- because the motor units are activated synchronically, the tetanic fusion can be reached only with frequency higher ( $> 20$  Hz) than the physiological one (about 10 Hz).

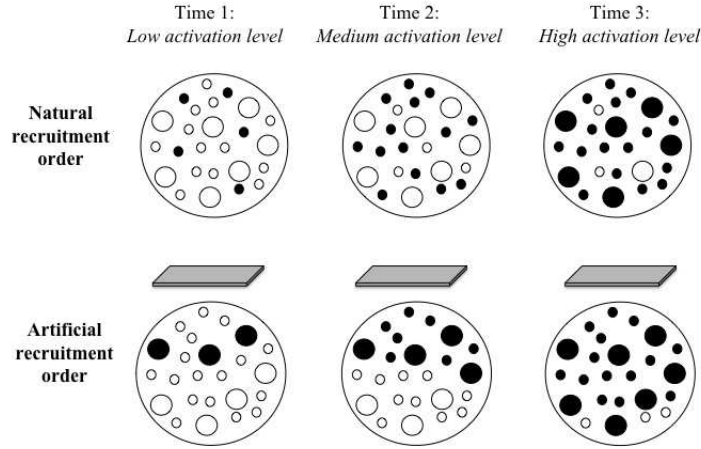


Figure 1.7: Comparison between physiological and artificial recruitment order of the muscular fibers.

The phenomena described determines an early fatiguing of stimulated muscle. This problem becomes even more relevant considering that the paretic muscles are characterized fibers with a reduced section (atrophy) and a conversion from type I to type II fibers (more fatiguable).

### 1.2.3 FES for motor recovery

The use of FES in rehabilitation is acquiring always more importance as it is effective not only to restore functional movements but also to produce enduring improvements in neuromuscular function that outlast the stimulation [35]. FES can be used in patients with hemiparesis who does not have enough residual motor control to take part in volitional, active, repetitive movement therapy. Clinical evidences suggest that the electrical stimulation of peripheral sensorimotor system may contribute to promote peripheral muscles health increasing muscle fiber cross-sectional areas and producing a shift toward fatigue resistant fibers [2]. The consequence is an improvement in atrophy and strenght.

A recent review [1] examined 24 randomized controlled trials involved in the assessment of the effectiveness of FES in improving functional motor ability and the ability to undertake activities of the daily living in hemiparetic patients. This review showed that electrical stimulation improves some aspect of motor recovery. In particular some evidence suggest that electrostimulation could be more effective in comparison with no treatment, placebo

treatment or conventional physical therapy. Moreover the review showed that the treatments were usually acceptable to participants as no statistical difference for withdrawal of participants between the different treatment existed. The authors concluded that, although a great variability between the dose of electrostimulation and the outcome measures between the studies, some encouraging evidence of the effectiveness of FES treatment are shown in literature.

The benefit of FES does not concern only the motor skills and other evidences are summarized in a review reported by Davis and colleagues [3]. The authors analyzed randomized controlled studies involved in the analysis of the effect of FES treatment and they showed some benefit concerning the enhanced cardiovascular and peripheral blood flow, an altered aerobic response to the exercise and some changes in bone mineral density. The main effects are summarized in Fig. 1.8.

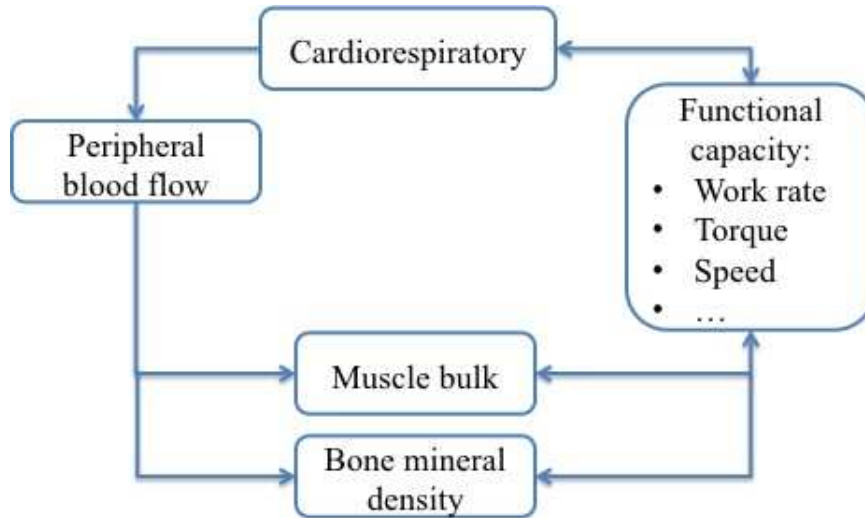


Figure 1.8: Schematic representation of the relationship between the fitness outcome following an FES-evoked exercise (adapted from [3]).

#### 1.2.4 FES for neuroplasticity and motor relearning

The term neuroplasticity refers to the capability of the brain to undergo structural and functional modifications. Different cortical reorganization mechanisms are triggered by natural or artificial stimuli. In fact plasticity may result after either a temporary or long term exposition to a biological stimulus (reactive or adaptation plasticity, respectively) or

it may become evident in the functional recovery of damaged neuronal stimuli (reparation or restorative plasticity) [36].

Cortical reorganization may occur mainly at two level. At local neuronal circuit level, plasticity is dependent on the intensity of afferent input. If for example a partial denervation occurs, synapses which have lost their connection degenerate while the remaining ones proliferate forming new links in place of the damage one. This form of plasticity appears to be fundamental in recovering of damage [37]. At synaptic level, it has been observed a long-term increase (potentiation) or decrease (depression) in the synaptic transmission effectiveness. The long term potentiation (LTP) mechanism take place thanks to Hebb-type synapses that are characterized by a reinforcement if pre-synaptic firing coincides with or is shortly followed by post-synaptic discharge. LTP was originally described in 1973 in the hippocampus of rabbit and was later observed in many other areas of mammalian CNS, including the anterior horn of the spinal cord [4].

The cortical reorganization mechanisms might explain the carry over effect observed after a training based on FES. Rushton [4] stated that “sometimes, after using the device for a while, patients may report that there is a “carry-over” effect. This may be short-lasting or long-lasting. There is a need to explain how a peripheral stimulus could restore the deficit resulting from a central lesion”.

He hypothesizes that electrical stimulation of a motoneuron generates an impulse that travels both in orthodromic (providing muscle stimulation) and antidromic (providing sensory feedback) directions (Fig. 1.9). This happens because the depolarization induced by electrical stimulation involves all the axons present into the nerve bundle.

As Rushton supposes that the horn cell can have Hebb-type synapses, if the antidromic stimulus and the voluntary command from the pyramidal tract reach simultaneously the anterior horn cells of the spinal cord, a synapses reinforcement take place. In healthy subjects this mechanism of reinforcement is physiologically provided while after a partial spinal cord lesion or a stroke the stimulus from the brain is reduced with a consequent synaptic weakening at the horn cell level. Electrical stimulation might reinforce the residual synapses that are activated in synchronization with the execution of movement (see Fig. 1.9).

Considering that the antidromic stimulus is absent in the traditional rehabilitation meth-

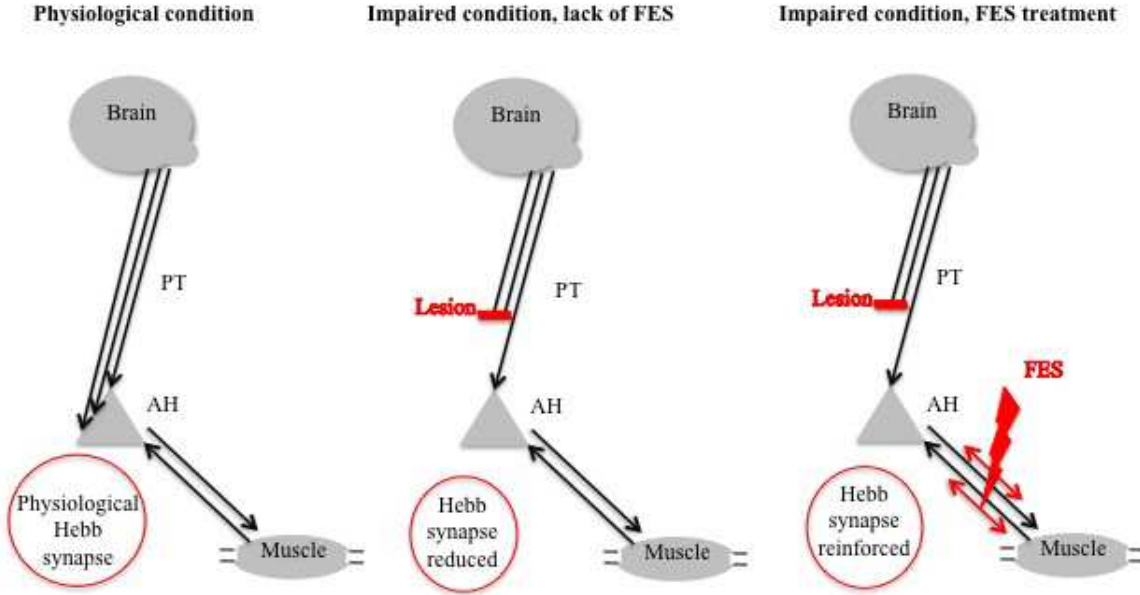


Figure 1.9: Reinforcement of the Hebb synapses mechanism. PT indicate the Pyramidal tract, AH indicate the anterior horn cells of spinal cord. The Hebb synapses are created between PT and AH. Adapted from [4].

ods (passive or active physiotherapy exercise), the Hebb synapses reinforcement is not achieved in this condition.

Some studies on neuroplasticity in children has been performed underlining that early experience has an enormous impact on brain development, behavior, learning and memory. In fact there are some evidences that the process responsible for neuroplasticity, based on preserving the neurons and synapses that are activated repeatedly while those that are not activated are pruned, continues massively till the age of 16 years. Later the mechanism is slow progressively down [38].

An evidence of the greater neuroplasticity in children is given by Benecke and colleagues [5]. They have observed that the cortical reorganization and, consequently the recovery of motor function, is simplified in patients who were damaged early in life. In fact after normal brain maturation the occurrence of a damage creates more permanent diseases. Moreover the reinforcement of the ipsilateral corticospinal pathway in the early brain damage group has been shown. Consequently, a remarkable residual motor capacity was observed in these patients. In the late damage group a less pronounced and slower ipsilateral pathway

was disclosed. The residual motor functions in the latter patient group was less striking. Anyway, only few studies are focused on FES for children rehabilitation although the encouraging neuro-physiological evidences.

### 1.2.5 Cycling induced by functional electrical stimulation

Clinical studies on central motor neuroplasticity support the role of goal-oriented, active and repetitive movement training of a paretic limb to enhance motor relearning [39], [40]. Moreover, as underlined in paragraph 1.2.4, the motor relearning mechanism is also reinforced by electrical stimulation. Thus, the application of FES during a cyclic movement could enhance the benefit observed in order to further improve the effectiveness of the rehabilitation treatment for lower limb impaired subjects [40].

The idea of an FES-induced cycling treatment (FES-cycling in the following) was born in the Eighties for the rehabilitation of spinal cord injuries (SCI) patients and has gained more and more interest in the following years being applied specially on post-stroke people [41]. In fact, one of the main goal of neuro-motor lower limb rehabilitation is the recover of locomotion that is improved by the use of FES [42]. In literature [43] two principle barriers are shown to explain limited utilization of FES in current locomotion training. First, the need to stimulate several muscle groups that the more impaired patients are unable to activate in a controlled manner while walking. The necessity of stimulating several muscle groups in concert with the gait cycle requires multichannel FES, which is expensive in terms of technology. Second, the reduced control of the balance impedes to perform the walking exercise in a safe way and prevents the home training.

A possible solution to these issues is to use a FES treatment during cycling. In fact the kinematic pattern of walking is very similar to the one of cycling [44]: both are cyclical, require reciprocal flexion and extesion movement and have alternating muscle activation of agonist/antagonist in a well-timed and coordinated manner.

Other advantage of the use of FES-cycling includes:

- activation of most of the lower limb muscles with a repeated task, thus enhancing motor relearning.



- symmetrical sensory feedback to the two legs, fundamental for hemiplegia and hemiparesis.
- safety and comfortable position during training, important for patients that usually have problems of balance.
- possibility of recreational and social exercise performing the treatment outside the clinical environment.
- cardio-vascular fitness, improved performing an aerobic exercise.

In addition to this, plenty of clinical benefit of FES-cycling are reported in literature, especially in terms of muscle strength, range of motion and cardiopulmonary system [45]. The devices needed for a FES-cycling treatment are schematically represented in Fig. 1.10, and they consist on a cycle-ergometer and a stimulator.



Figure 1.10: Schematic representation of the FES-cycling system.

The subject is normally seated (eventually on a wheelchair) in front of the ergometer with ankle orthoses that avoid dorsi-plantar flexion and internal-external rotation and inversion-eversion. The stimulator receives the information of the crank angle from the ergometer and sends the appropriate sequence of muscle stimulation synchronized to it. Two kinds of exercise can be performed: the iso-tonic and the iso-kinetic training. The

first one can be realised maintaining a constant crank resistance (and consequently a constant speed) during the training. The second one is achieved maintaining a constant pedaling cadence. In order to keep the cadence unvaried, the ergometer is motorized and it assists the pedaling guaranteeing a minimal cadence value. Safety features of the recent motorized ergometers avoid to injure the subject by forcing a limb movement in presence of a strong spasm [46].

Different muscle group can be stimulated, depending on the target pathology. The extensors and the flexors of the knee (quadriceps and hamstrings) are typically stimulated. Other target muscles are the hip extensor (gluteus maximus) and the dorsal and plantar flexors (tibialis anterior and surae muscles) [47]. In any case, work and power output during pedaling is mainly sustained by quadriceps followed by the hamstring and then by gluteus maximus.

Many studies have focused on the optimal stimulation strategy in order to provide an effective stimulation pattern. A possible approach [48] is to test the static force produced at set angles around the “likely” positions for each muscle group. This approach applies force statically measured to a dynamic system. Another proposal [49] is to define the angular range of stimulation for each muscle on the basis of the electromyographic activation of muscles during voluntary pedaling of healthy subjects. This assures that the muscles are stimulated according to a physiological muscular strategy. A third possibility proposed by Ferrante and colleagues [6], [50] is to evaluate the stimulation pattern measuring the torque produced by each muscle during a stimulation maintained for the whole cycle of the crank. The ranges of positive torque were then matched with the physiological muscular activation obtained with electromyographic signal during voluntary pedaling of healthy muscles. The angular ranges of useful functionality of each muscle are identified as the one within the healthy muscular activation with a positive torque contribution. The main advantage of this approach is that the muscles are stimulated according to the physiological activation strategy, providing the patient afferent input correctly correlated with the movement.

In recent years the application of FES-cycling for lower limb rehabilitation of hemiparetic subjects has been increasingly used.

A randomized control trial on 35 post-acute hemiparetic subjects has been performed by

Ambrosini and colleagues [51] to assess the effectiveness of FES-induced cycling with respect to passive cycling in lower limb rehabilitation. Patients were randomly allocated into two groups receiving cycling training induced by FES (FES group) or passive cycling training with FES placebo (placebo group). In the first group four muscles (quadriceps, hamstrings, gluteus maximus and tibialis anterior) of each leg were stimulated using surfaces electrodes. The 4 week-intervention consisted in 20 sessions, lasting of 25 minutes each, with 5 minutes of passive pedaling, 15 minutes of FES-cycling or placebo FES-cycling and 5 minutes of passive pedaling. The results obtained strongly supported that a four week intervention of FES-cycling training improves symmetry, mechanical work and motor coordination in post acute hemiparetic patients.

The possibility of restoring locomotion ability after an FES-cycling treatment has been also studied by Alon and colleagues [43]. They performed a study including 10 stroke subjects that was trained 3 times a week for 8 weeks with an 30-minutes FES-cycling training with voluntary contribution. Stimulated muscle were quadriceps, hamstring and dorsal-plantar flexor. The results shown an improved locomotor capability in terms of gait velocity and time to stand up, proceed to walk 3 m, turn around, walk back and sit down. Moreover the peak pedaling power increased during the intervention.

### **1.2.6 FES-cycling in the rehabilitation of hemiparetic young subjects**

As many studies [41], [43], [51] demonstrate the effectiveness of FES-cycling training in reducing weakness and improving motor recovery in hemiparetic adults, only few evidence has been shown for younger subjects. This field of research is very interesting because, as told in paragraph 1.2.4, the benefits shown on adults could be further enhanced in younger population thanks to the greater plasticity and flexibility of their central nervous system [9], [38].

A study of feasibility and an evaluation of the immediate effects of FES-cycling treatment on CP adolescents was performed by Harrington and colleagues [8]. They have recruited five participants (age 12-14 years) affected by moderate or severe cerebral palsy. The subjects underwent to a of FES-assisted cycling in which bilateral quadriceps muscles were activated using surface electrodes. During the training information about cycling cadence, power output and pedaling variability were collected. Their results assessed that

the treatment was well tolerated and some improvement could be obtained. In fact the cycling performance when accomplished by FES showed increased cadence, power output and decreased pedaling variability compared to volitional cycling without FES assistance. A similar work [52] on four CP subjects further confirms the results, assessing also that the FES training allowed subjects to work at sufficient levels to achieve increased heart rate and maximum oxygen consumption.

A recent study [9] on two CP infants has shown some results with a FES-cycling treatment performed 3 times a week for 7 weeks. Each session includes 30 minutes of training composed by 5 minutes of passive pedaling, 20 minutes of active pedaling (FES) and 5 more minutes of passive pedaling. Four muscles for each leg (quadriceps, medial hamstring, gluteus maximus and tibialis anterior) were stimulated. Improvements in terms of reduction of the co-contraction of agonist-antagonist muscles, symmetrical cycling and gait strategy have been shown giving some evidences of the effectiveness of FES-cycling for CP rehabilitation.

Fowler and colleagues [10] studied the effect of cycling training (with no FES contribution) on sixty-two children (7 to 18 years) with spastic diplegic CP. Participants were randomized to a cycling or no-intervention group. The first group was trained with 30 sessions of cycling over 12 weeks. After the intervention no significant improvements were obtained for both the groups thus suggesting that the eventual results obtained after FES-cycling training should be completely ascribed to the electrical stimulation.

In conclusion, the published studies do not state definitely the effectiveness of FES-cycling treatment in the rehabilitation of hemiparetic young subjects, although the results obtained are encouraging. Further investigations are needed to confirm the role of cycling induced by FES treatment in promoting motor recovery in young hemiparetic subjects.

### **1.3 Instrumental evaluation of motor impairment**

To evaluate the effectiveness of a rehabilitation training an appropriate set of outcome measures that assess the motor performance should be defined.

Clinical scales have been traditionally used to investigate various aspect of the subjects conditions but they are inherently not repeatable, operator-dependent and often qualita-

tive.

In the last years the interest in methods that provide quantitative evaluations is increasing because a rigorous instrumentation assessment could produce results with maximum accuracy [53].

An evaluation of the possible improvement of motor impairment after the cycling training could be performed assessing both pedaling and locomotion ability.

### 1.3.1 Gait analysis

One of the most important options to the clinicians for monitoring the motor problems experienced by hemiparetic children and adolescents is the gait analysis.

The gait analysis is a standardized technique of movement analysis that give quantitative information on the gait movement. The conventional gait test is performed considering a multi factorial approach as at the same time it analyses kinematics, dynamics and electromyographic variables [13].

The locomotion is a repetitive process that can be subdivided in “stride cycle”. The distance that occurs between the feet during a single stride cycle is called step length while the distance covered by a foot during the stride cycle is the stride length [13]. Moreover the stride cycle can be subdivided into two main phases: the stance phase that employs the 60% of the whole cycle and the swing phase for the remaining 40%. (see Fig. 1.11).

During the stance phase some sub-phases with important functional meaning can be highlighted. These are the initial contact, the loading response, the mid stance, the terminal stance and the pre-swing. On the other hand the swing phase can be divided in initial, mid and terminal swing.

The initial contact (IC) is the instant of foot contact to the ground and is immediately followed by the loading response when occurs the weight shift. The mid-stance is the time interval from lift of the contralateral extremity from the ground to the point where the ankles of both extremities are aligned in the frontal plane. The terminal stance follows, till the moment prior to initial contact of the contralateral extremity. The double support is maintained during the whole pre-swing phase [12].

The events that occur during the swing are the lifting of the limb from the ground to the position of maximum flexion during the initial swing phase, then the knee flexion to

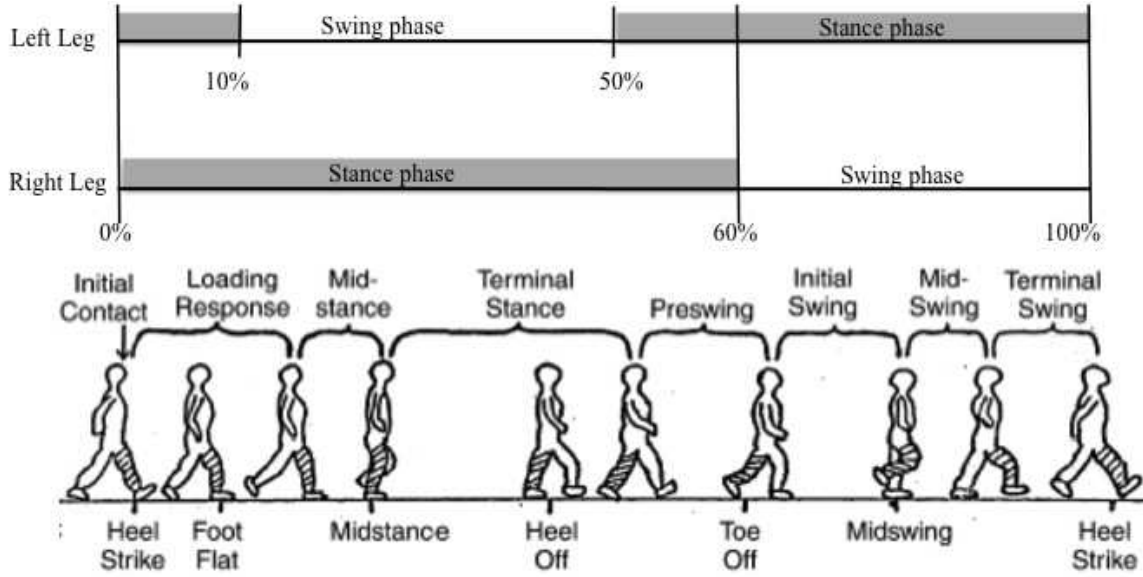


Figure 1.11: Schematic representation of temporal phases of a stride cycle (adapted from [12], [13]).

vertical tibia position in the mid swing and finally the terminal swing phase that ends with the initial contact [12].

Hemiparesis diseases produce a number of gait deviation [14] concerning the following aspects:

- Spatio-temporal parameters: firstly the gait speed is decreased in proportion to the severity of the pathology. Tilson and colleagues [11] suggested that gait speed can be significantly correlated with the level of disability in people with stroke. They divided the stroke population into three categories: people walking at speeds  $< 0.4$  m/s were household ambulators, people walking at speeds included between 0.4 m/s and 0.8 m/s were limited community ambulators, and people walking at speeds  $> 0.8$  m/s were able to walk in the community without substantial limitations.

Moreover a proportionally longer stance phase is usually showed, especially for the affected limb and a longer double support period caused by an early foot contact by unaffected side.

- Kinematic characteristics: concerning the hip, a decreased flexion at IC, an increased flexion at toe off and a decreased flexion during mid swing can be highlighted. The knee shows and increased flexion at IC and a decreased flexion at toe off and mid

swing. Finally the ankle usually presents more plantarflexion at IC and mid swing and less plantarflexion at toe off (see Fig. 1.12).

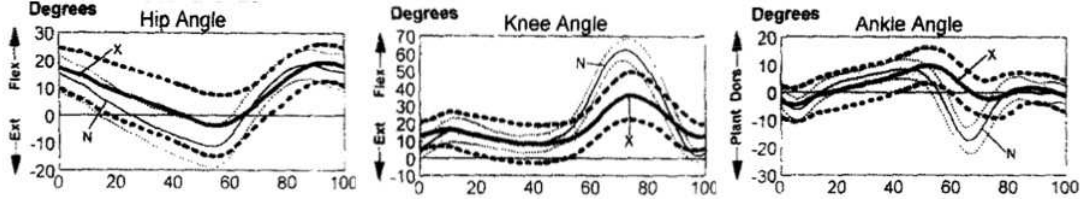


Figure 1.12: Mean and standard deviation of relative joint angles for 30 subjects with hemiparesis (X) compared with healthy population (N), adapted from [14].

- Kinetic characteristics: reduced moments and power are generally produced. The ground reaction force is reported with three kind of patterns: the first one is typical of able-bodied with two peaks, one during heel contact phase and the other during pushing off phase, the second with a continue plateau but no discernible peak and the third with a single peak in mid stance. Concerning the joint power, the most relevant deviation are observed in the ankle power that shows a smaller peak of ankle plantarflexors during push off phase.

### 1.3.2 EMG signal analysis

The electromyographic (EMG) signal is a representation of the electric potential field generated by depolarization of the fiber membrane of the more superficial muscles during a contraction [54]. The features of the detected signal are strongly dependent from the properties of the tissues (called volume conductor) that the signal has cross. In particular the volume conductor behave as a spatial low-pass filter as it attenuates more the high spatial component of the signal that are generated relatively far from the detection electrodes [55]. The amount of attenuation depends on the relative distance between signal sources and detection electrodes, the spatial frequency content of the signal and the geometry of the detection electrodes.

For the EMG signal detection, intramuscular or surface electrodes can be employed. The intramuscular electrodes require the insertion of electrodes directly into the muscles allowing the detection of electric potential very close to the source, so as action potential of the

different motor units can be separated. Although it is a quite invasive measure, it can be preferred because it allows a bigger selectivity of the source. On the contrary the surface recording is affected by a reduction of the signal intensity and the effect of spatial low-pass filtering of the tissue separating signal source from the electrodes becomes relevant [54]. In order to partially compensate the spatial filtering as well as to reduce the common mode components caused by technical interference (e.g. a power line), the surface signals are usually recorded as a linear combination of the signals detected at different electrodes. The simplest form is the differential detection, obtained with a bipolar placement.

The surface electromyography (sEMG) has some advantages: it is a less invasive technique and it provides information more directly correlated to the mechanical outcome as it is correlated with large mass of muscle tissue [56].

Among the most relevant problems related to the sEMG there are the motion artifact and the crosstalk. The first one is due to the movements of electrodes and/or cables and can be reduced fixing carefully all the cables and by using appropriate device. The crosstalk phenomenon is caused by the overlap between the EMG signals coming from two different muscles located nearby. It is particularly confounding as the obtained signal has the characteristics of the signal generated by a single muscle and so the timing of activation of the target muscles can be misunderstood. However the potential generated by a source decays rather fast in space and therefore crosstalk should be a limited problem if the location of the electrodes and the dimension of the target muscles are appropriated. The electrode configuration as well can be important. In fact a comparison between the EMG signal obtained with monopolar and bipolar configuration of the electrodes was shown by Roeleveld and colleagues [15] for both a superficial and a deep motor unit (see Fig. 1.13). In this study the intramuscular detection of motor unit potentials were used as a trigger for an averaging process aimed at extracting the surface potential in different locations over the muscle. As the magnitude of the recorded potential is dependent on the radial position between the motor unit and the the recording electrode, the monopolar (far-away reference) configuration is less selective [15].

In the past there have been many attempts to investigate crosstalk. The first study that report evidence of the crosstalk was in 1949 by Denny-Brown [57], who observed en electrical activity above denervated muscles when neighbouring muscles are intensely activated.



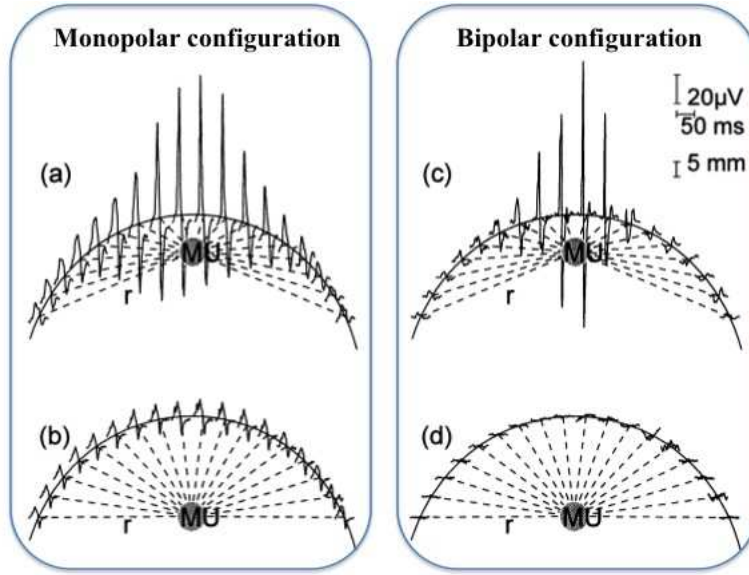


Figure 1.13: Activation potential recorded in 18 sites with different radial distances  $r$  from superficial (a,c) and deep (b,d) motor unit. Adapted from [15].

Later, a number of study has been conducted with the purpose of identifying a method to assess the presence of crosstalk. Morrenhof and Abbink [58] assumed that minor shape changes occurred between the signal generated by the same source and detected in different locations over the skin. Thus they proposed to use a cross-correlation coefficient between signals as indicator of the crosstalk. Recent findings have given evidence that this method is not appropriated [54].

Other authors [59] proposed to assess the crosstalk electrically stimulating a muscle and detecting the electrical activity above the nearby muscles. Their results obtained on lower limb muscles of 12 healthy subjects showed that a relevant crosstalk takes place between tibialis anterior and peroneus brevis while a less notable result is found between tibialis anterior and soleus. Results of another study [55] highlighted that the stimulation of the vastus medialis generate a strong signal on vastus lateralis while a smaller signal was detected on rectus femoris and on hamstrings.

Finally, literature agrees that crosstalk does not exceed 10%-15% of the overall signal contents and it can be minimized choosing an appropriate size of the electrodes conductive area and the appropriate inter-electrode distance. In order to supply a standard for the studies that differently employ the sEMG, a European concerted action in the Biomed-

ical Health and Research Program (BIOMED II) of the European Union developed in 1999 the SENIAM project (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles) [60]. SENIAM collects some recommendations concerning the electrodes characteristics (shape, size, inter-electrode distance, material), the preparation of the subject and the location of the electrodes useful to minimize the crosstalk problem.

The EMG signal can be used to assess possible variation in the activation timing and profile shape of muscles involved in a functional task.

During the gait analysis the EMG signal of lower limb muscles is often recorded assessing the muscular activation during locomotion. Hemiparetic subjects are characterized by some deviations. In fact, although a great inter individual variation Knutsson and Richards [61] classified the hemiparetic population on the base of the EMG signal into three main categories. The first one presented hyperactive stretch reflexes leading to premature activation of the calf muscles that were stretched following IC and weight acceptance. The second one was characterized by low level of muscles activities, especially the distal muscular groups with the effect of a reduced ability to generate power and to stabilize the gait. Finally, the third group exhibited motor control impairment due to excessive and stereotyped co-activations of several muscle groups, disturbing the normal sequences.

Another study on hemiplegic lower limb was carried out quantitatively relating the extent of EMG activation timing abnormalities to the level of motor performance during pedaling [62]. The study was performed comparing the muscle performance of the plegic limb of 15 post-stroke patients with an healthy control group (12 people) during a cycling exercise. In Fig. 1.14 the main results of the study are shown. In the figures the revolution has been divided in 4 phases: phase I coincided with limb extension (foot moving away from pelvis) and anterior limb motion (with respect to the trunk/pelvis axis), phase II coincided with limb extension and posterior motion, phase III coincided with limb flexion (foot moving towards pelvis) and posterior motion, and phase IV coincided with limb flexion and anterior motion. For each phase, the rectified EMG was integrated (IEMG) and expressed as a percentage of the total IEMG in a cycle.

Their results showed a prolonged vastus medialis excitation and a “phase-advanced” (meaning both onset and offset occur earlier in the crank cycle than normal) rectus femoris

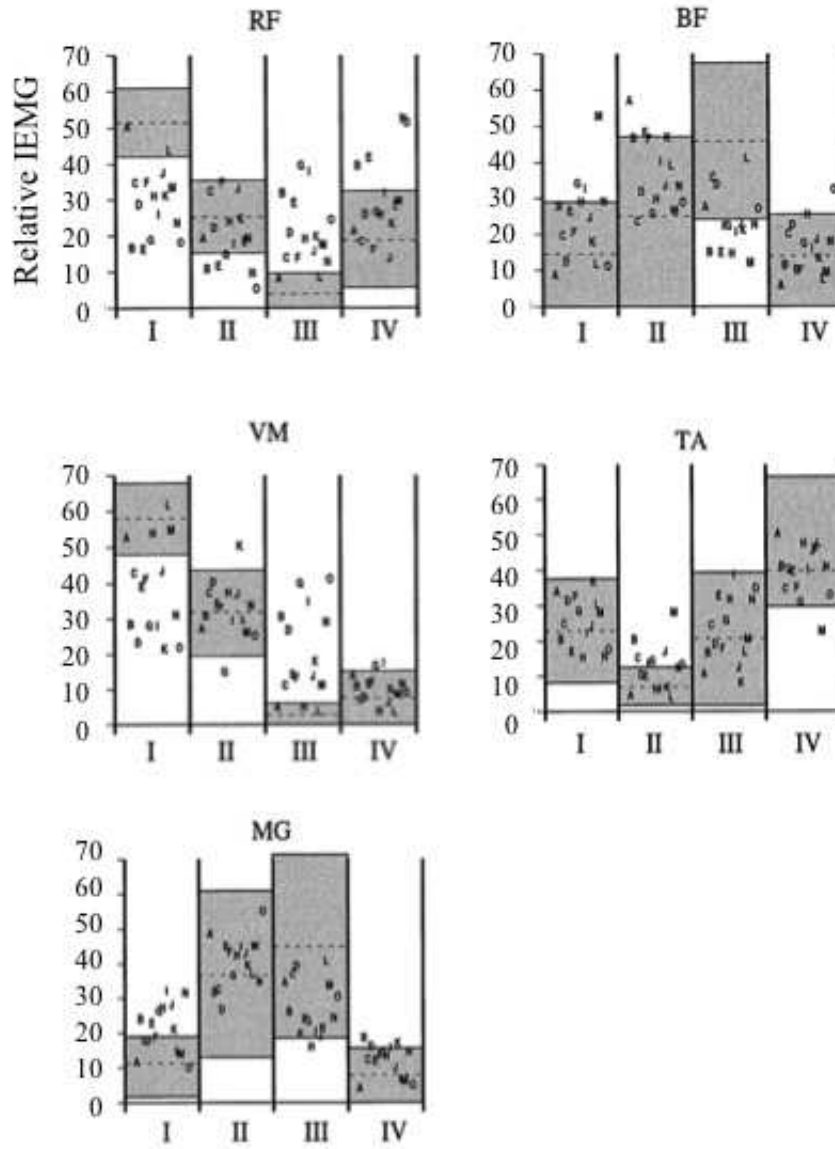


Figure 1.14: Relative IEMG (%) for five muscles (MG=medial gastrocnemius; RF=rectus femoris; TA=tibialis anterior; VM=vastus medialis), showing individual subjects (indicated with letters A-O) compared with control subjects (shaded region) represented by the mean activity (dotted line)  $\pm 2$  SD.

excitation. The biceps femoris also exhibited phase-advanced excitation while the muscles crossing the ankle (tibialis anterior and gastrocnemius medialis) were both early initiated; their results were less severely impaired than the others.

The most interesting result of the study concerned the relationship between EMG tim-

ing abnormalities and limb movement. In fact it underlined that prolonged excitation was observed in the muscles that were normally excited only during extension (vastus medialis and partially rectus femoris) while the muscles involved in both limb extension and flexion (biceps femoris, gastrocnemius medialis and partially rectus femoris) showed phase-advance excitation.

## 1.4 Aim of the work

The present work is focused on the investigation of the feasibility and the effectiveness of an FES-augmented volitional cycling training in improving gait and lower limb motor function on a restricted group of hemiparetic adolescents.

This training has been selected since it involves a functional movement and it can be safely performed even in a domestic setting. Moreover the volitional contribution to the pedaling could be important as, according to some studies, if it is synchronized with the electrical stimulus, it reinforces the synapses augmenting the cortical reorganization.

Previous works on adult neuro-motor impaired subjects suggested the effectiveness of this intervention in improving motor recovery but only few studies have been focused on young population. When FES-augmented volitional cycling training is applied on young subjects, the neuroplasticity can be maximally exploited, thanks to a greater flexibility of their central nervous system.

In order to evaluate if the functional motor recovery occurred in the patients, some assessment tests including clinical and biomechanical measures are required.

In the study design, this tests are planned at four different time points. In particular two assessment are performed before the treatment allowing to evaluate if changes occurs independently from the training (e.g. for the physiological growth) and verifying the repeatability of the results intra-session. Moreover with the two tests after the treatment, the “carry-over” effects of neuroplasticity can be studied analysing both short-term and long-term effects.

The clinical assessments are aimed at the definition of the subjects’ functional deficit, evaluating the motor condition with observational and qualitative tests.

Since one of the main goal of lower limb rehabilitation is the restoration of the walking

capability (see paragraph 1.2.5), possible improvements during locomotion are quantitatively evaluated with gait analysis.

Furthermore, as the FES-cycling training is based on a pedaling movement, the performance of the subjects during cycling is also assessed. Particular interest is addressed to the mechanical work produced by each leg and the muscular activation timing.

The present work is mainly focused on the data acquisition and analysis of the pedaling test while the clinical evaluation and the gait analysis are standard tests whose methods are already widely discussed in literature.

In the following chapters an overview of the whole results is anyway discussed in order to have a global evaluation of the motor recovery of the subjects.

In particular in Chapter 2 the study design and the intervention planned for each subject are presented. Moreover the methods used during the assessment tests, especially concerning the pedaling, are widely discussed.

Chapter 3 reports details on the recruited patients at baseline and on the treatment performed by each on them. The following sections present and discuss the results obtained during the assessment tests. In particular a first part shows the data concerning a group of healthy subjects recruited as control group for the pedaling test. Then, as the study is a case series, the results of each subject are presented singularly.

Finally, Chapter 4 provides a last overview on the problem dealt and on the results of the thesis concluding with limitation and future developments that could be explored in future works.

## Chapter 2

# Material and Methods

This work has been performed within a collaboration between the Developmental Neurology Unit of "Carlo Besta" Neurological Institute Foundation, the "NeuroEngineering And medical Robotic Laboratory" (NEARLab) and the "Luigi Divieti posture and movement analysis Laboratory" (Divieti Lab), both of the Department of Electronic Information and Bioengineering of Politecnico di Milano.

### 2.1 Participants and design

The participants were recruited from the Developmental Neurology Unit of "Carlo Besta" Neurological Institute Foundation in Milan.

The inclusion criteria were:

- Age between 10 and 18 years.
- Diagnosis of acquired hemiparesis
- Possibility of autonomous walk
- Low spasticity level (Modified Ashworth Score [63] inferior than 2)
- Lack of articular limitations
- Lack of surgery or pharmacological treatments with Botulinum toxin
- Lack of electrode allergy

- Tolerance to stimulation
- Intellectual level major or equal to 70
- Family compliance

All families received an information sheet and were provided with a written informed consent. The medical ethic committee of Neurological Institute Besta approved the research protocol.

To assess the effectiveness of the treatment, the subjects were tested in four different sessions, two before the FES-cycling training and two after.

Before the treatment, the assessment tests were performed twice at a distance of 7 weeks. During this “observation phase” the subjects were supposed to perform their daily life activities. The two assessment sessions, oPRE (observation PRE) and PRE in the following, allowed to monitor the trend of neuromotor variation due to the physiological growth, particularly marked during the considered age range.

The assessment tests after the treatment (POST and FU in the following) were performed in order to evaluate both short-term and long-term effect of the FES-cycling trial. In fact the POST test was performed immediately after the treatment while the follow-up (FU) session was carried out after 12 weeks during which the subjects had conducted their every-day life activities without any particular treatment. The timeline of the study design is summarized in Fig. 2.1.

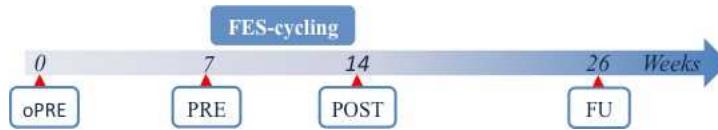


Figure 2.1: Timeline of the assessment tests for each subject. The assessment test are indicated as oPRE, PRE, POST and FU.

## 2.2 Intervention

All participants were trained 3 times a week for 7 weeks, receiving a total of 21 sessions. Each session consists in an iso-kinetic exercise lasting 30 minutes and composed as follows:

- Worm-up phase: 5 minutes of passive pedaling during which the motor of the ergometer moved the legs of the subject at a speed of 40 revolution per minutes (rpm).
- Stimulation phase: 20 minutes of active stimulation of the muscles synchronized with voluntary pedaling. The speed provided by the motor was decreased and the subjects were asked to pedal at a fixed velocity of 40 rpm. The pedaling resistance provided from the ergometer was adjusted on each subject in order to allow a smooth movement.
- Worm-down phase: after the stimulation 5 more minutes are required to cool-down the muscles. The pedaling movement was performed again from the ergometer while the subject is seated passively in front of it.

During the intervention a MOTOMed Viva2 ergometer (Reck GmbH) and a RehaStim stimulator were used. The surface stimulation electrodes (Alexgaard Manufacturing Ltd) were used depending on the dimension of the muscles of each subjects, choosing different electrodes size and shape (oval 1.5"x2.5", rectangular 1.3"x2.1", rectangular 2"x3.5"). Accordingly to the indication from literature (see paragraph 1.2.5), the four muscular groups stimulated were quadriceps, gluteus maximus, hamstrings and tibialis anterior. The final setup can be observed in Fig. 2.2.

The stimulator was directly linked with the ergometer that measured with encoders the crank angle. According to [50] (see paragraph 1.2.5 for further informations) the FES is delivered to the muscles within angular ranges that guaranteed a physiological activation strategy, providing the patient afferent input correctly correlated with the movement. The stimulation strategy used in the training is reported in Tab. 2.1.  $0^\circ$  is referred to the crank angle that correspond to the maximum flexion of the left hip. The values of pulse width and stimulation frequency were fixed for all the subjects and muscles at  $300 \mu s$  and 20 Hz respectively. On the contrary, the values of pulse amplitude were set for each subjects and muscles in order to induce a visible muscular contraction without causing pain. As the subjects did not perform any electrical stimulation before the training, the values of pulse amplitude were adjusted during the first three sessions of training and then kept constant. The subjects were assisted during the training by an operator that supervised the execution of the exercise and verified the maintenance of the speed.



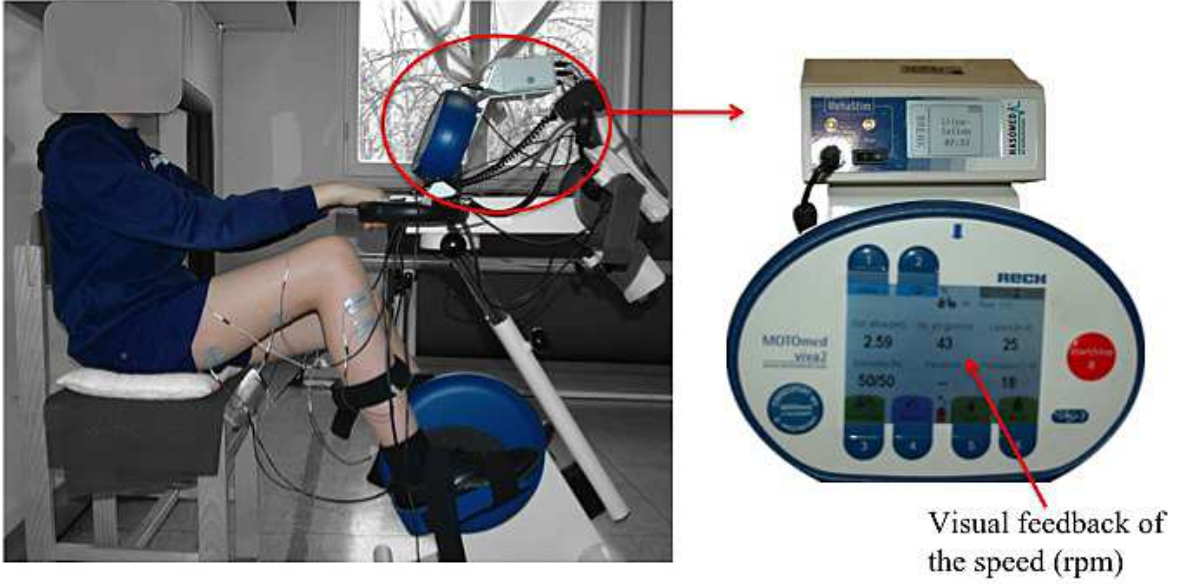


Figure 2.2: Experimental setup used for the FES-cycling training. A visual feedback of the speed was provided to the subject during the 20 minutes of FES augmented volitional pedaling.

Muscle stimulated	Start (degree)	Stop (degree)
Right quadriceps	150°	280°
Right gluteus maximus	240°	340°
Right hamsting	280°	50°
Right tibialis anterior	50°	150°
Left quadriceps	330°	100°
Left gluteus maximus	60°	160°
Left hamsting	100°	230°
Left tibialis anterior	230°	330°

Table 2.1: Angular range of stimulation for the stimulated muscular groups. 0° is referred to the crank angle that correspond to the maximum flexion of the left hip.

### 2.3 Assessment tests and outcome measures

Three kinds of assessment tests was performed during for each of the four sessions. During these appointments, a number of outcome measures were collected.

### 2.3.1 Clinical evaluation

To assess the functional deficit level during walking the Winter scale [64] was used. This classification, widely used for hemiplegic subjects, was based on goniometric data in the sagittal plane for hip, knee and ankle.

Within their study Winter and colleagues subdivided a group of young hemiplegic patients in four subgroups assigning a score from I, in case of mild deficit, to IV, corresponding to severe deficit. More details are reported in Tab 2.2.

Definition	Winter Scale
Insufficient ankle control in swing phase with foot-drop	I
Insufficient ankle control in swing phase with foot-drop and ankle plantar flexion in stance phase, for hyperactivity and/or shortening of calf muscles, with recurvatum of the knee	II
Reduction of knee flexion motion in the swing phase due to quadriceps overactivity	III
Reduction of knee flexion motion in the swing phase due to quadriceps overactivity and flexed position of the hip with reduced range of motion	IV

*Table 2.2: Winter classification of hemiparesis disease.*

The gross motor function measurement (GMFM) was used to assess the gross motor skills [65]. The gross motor skills involves the ability of large muscular groups of the body that enable function as walking, standing, sitting and postural control. The gross movement are acquired during the early childhood as part of the child's motor development and they continue to be refined till adulthood.

The GMFM is a standardized observational measure that was developed and validated to measure change in gross motor function over time in children and adolescents with

cerebral palsy [66]. It is based on 88 items that span the spectrum from activities in lying and rolling up to sitting, crawling, standing, walking, running and jumping. An operator is asked to assign a score between 0 (do not initiate the skill) to 3 (complete the skill) for each of the 88 items of the test. If a function cannot be tested the “Not Tested” key is assigned. The final score is obtained as percentage of the maximum score obtainable (from 0% if no gross motor task is completed to 100% if every gross motor tasks are completed). A further clinical evaluation of hemiparesis involved the distal selective motor voluntary control assessed with a Boyd test [16]. The subjects are asked to sit with hip flexed and knee comfortably extended, able to see their feet. The task is to dorsiflex each foot individually towards a target established by an operator. Observing the behaviour during the test, a score between 0 and 4 is assigned to the subjects. In Tab. 2.3 the definition associated to each score is described. The Boyd test is useful because it assess possible

Definition	Boyd Test Score
No movement when asked to dorsiflex the foot	0
Limited dorsiflexion using mainly extensor hallucis longus and/or extensor digitorum longus	1
Dorsiflexion using extensor hallucis longus, extensor digitorum longus and some tibialis anterior activity	2
Dorsiflexion achieved using mainly tibialis anterior, but accompanied by hip and/or knee flexion	3
Isolated selective dorsiflexion achieved, through available range, using a balance of tibialis anterior activity without hip and knee flexion	4

Table 2.3: Boyd Test score, adapted from [16].

improvement in selective motor control that are symptoms of a better dorsiflexion and foot

clearance in swing phase of gait cycle. This improvement of dorsiflexion may correspond with an improved activation of tibialis anterior [16].

The fourth clinical assessment performed was the Observational Gait Scale (OGS) that give an evaluation of the kinematics pattern of the gait movements. In order to have a more reliable test, the subjects are filmed with a video camera during the walking exercise and the operator assigns the score based on the images recorded. A description of the ability that corresponds to each score is given in Tab. 2.4. The total score of OGS is obtained as a sum of the single score for each item. An healthy subject would collect 22 points [16].

In order to evaluate the level of spasticity of the muscles involved in the training, the modified Ashworth scale was also applied [63]. The spasticity causes a speed dependant resistance to stretch where a lack of inhibition results in excessive contraction of the muscles. The resistance to stretch and the muscular tone are evaluated assigning a score between 0 and 4. Tab. 2.5 describes the guide lines to assign each score. The spasticity is a relevant problem for hemiparetic patients and the FES-cycling is delivered only on patients with low spasticity level (see paragraph 2.1). Literature studies [67] report that the presence of relevant spasms preclude the use of artificial electrical activation of the muscles in order to avoid unwanted reflex activation in patients with high levels of spasticity.

### 2.3.2 Gait analysis

The gait analysis sessions were performed at “L. Divieti” Laboratory of Electronic Information and Bioengineering Department of Politecnico di Milano.

The equipment used for the acquisition consisted of:

1. An optoelettronic System ELITE 2002 (BTS SpA) that uses 8 video cameras working in the near infrared wavelength, with a sampling frequency of 100 Hz. The cameras allow to measure the three-dimensional coordinates of some catarifrangente elements (markers) fixed with biadhesive tape to points of repere on the body of the subject according to the Davis protocol [68]. In order to minimize the motion artifact, the markers are positioned directly on the skin in areas where the distance between the

Gait parameter	Definition	OGS
Knee position in midstance	Crouch >15	0
	Crouch 10-15	1
	Crouch <10	2
	Crouch Neutral	3
	Recurvatum <5	2
	Recurvatum 5 - 10	1
	Recurvatum >10	0
Initial foot contact	Toe	0
	Forefoot	1
	Foot-flat	2
	Heel	3
Foot contact at midstance	Toe/toe (equinus)	-1
	Foot-flat/early heel rise	0
	Foot-flat/no early heel rise	1
	Occasional heel/foot-flat	2
	Heel/toe (normal roll-over)	3
Timing of heel rise	No heel contact (fixed equinus)	0
	Before 25% stance (very early)	1
	Between 25-50% (slightly early)	2
	At terminal stance	3
	No heel rise (after foot-flat)	0
Hindfoot at midstance	Varus	0
	Valgus	1
	Neutral	2
Base of support	Frank scissoring	0
	Narrow base (poor knee clearance)	1
	Wide base	2
	Normal base (width of shoulders)	3
Gait assistive device	Walker with assistance	0
	Walker (independent)	1
	Crutches, sticks	2
	None, independent for 10 m	3
Change	Worse	-1
	None	1
	Better	2

Table 2.4: *Observational Gait Scale test. The total score of a healthy subjects is 22. Adapted from [16].*

Definition	Ashworth Scale
Lack of spasticity	0
Moderate spasticity only at the end of the movement	1
Moderate and continuous spasticity during less than half of the movement	1+
Moderate and continuous spasticity during all the movement	2
Relevant spasticity with severe limitation of the movement	3
Irreducible spasticity	4

*Table 2.5: Modified Ashworth classification of grading spasticity.*

bone and the marker is minimal.

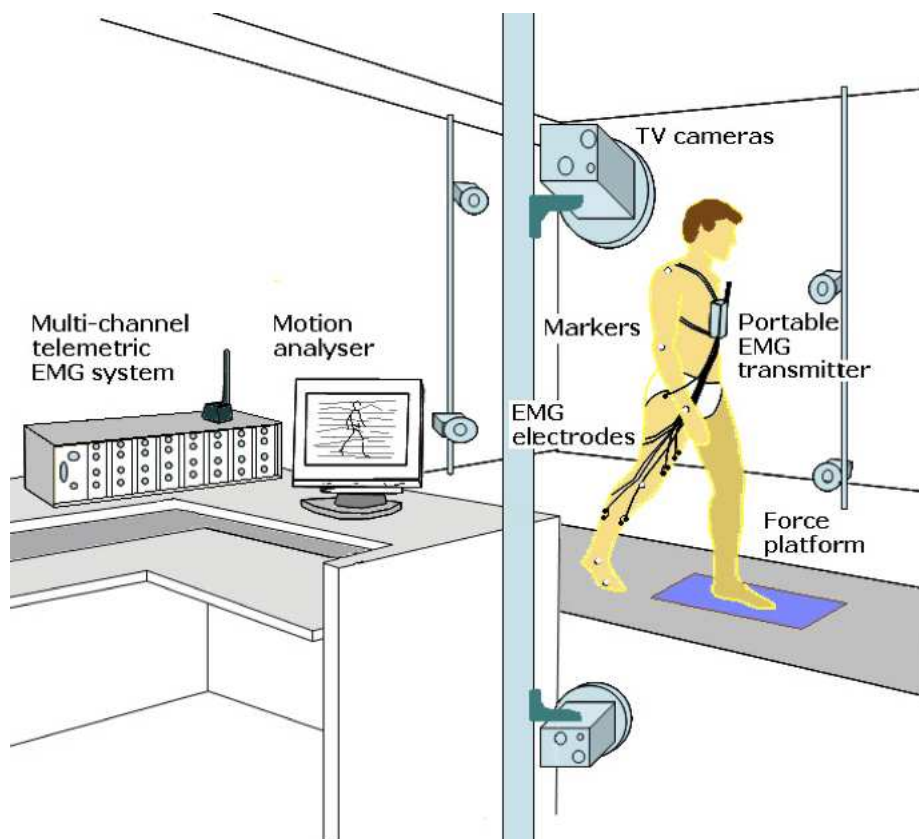
During the test the markers are lighted by some LED (Light-Emitting Diodes) in a coaxial position with respect to the cameras. The infrared rays are reflected by the catarifrangente element and thus recorded by the cameras. The position of the marker is well distinguished thanks to software that measures the position of the centroid of the light area produced by at least two cameras. Based on the measurement of the coordinates of the markers a software compute spatio-temporal parameters (speed, stance and swing time, step length and others) and kinematics (angles of flexion-extension, abdo-adduction and extra-intra rotation of the main joints) of the movement of the physical segment where the markers have been positioned.

- Two force platforms suited to measure the ground reaction forces were included. The platforms are based on force transducers that are deformed proportionally to the applied force. The centre of pressure (CoP) is the position of the centroid of the system of forces applied to the ground and is computed in order to know the system

of forces exchanged to the ground. Knowing the CoP and the kinematic data (by means of the ELITE system) it is possible to calculate the moments and the powers at the joints obtaining information about the kinetics of the movement.

3. A traditional system for the video shooting of the movement (Video Controller, BTS, Italia), positioned on both the frontal and sagittal plane. The data are synchronized with the kinematics and dynamics.

In Fig 2.3 the instrumentation used for gait analysis are shown. [69].



*Figure 2.3: Instrumentation used for Gait Analysis.*

Before each session, anthropometric measurements were recorded and 18 markers plus four bars were positioned on the subjects (Davis protocol). Each patient was asked to walk along the platform at his natural speed for at least four or more repetitions. After each session, the most repeatable test was chosen to be analyzed. The more relevant outcome measures extracted were:

- Spatio-temporal parameters: Mean velocity during gait ( $V$ ), step length of paretic and healthy limb ( $L_{PL}$ ,  $L_{HL}$  respectively) and symmetry index ( $SI$ ) computed as the ratio between paretic and healthy step length ( $SI = \frac{L_{PL}}{L_{HL}}$ ).
- Kinematics: angular values and range of motion (ROM) of ankle, knee and hip on frontal, sagittal and horizontal planes.
- Kinetics on sagittal plane: moment and power produced at ankle, knee and hip in the sagittal plane.
- Vertical Forces exchanged to the ground.

To evaluate the results of the patients, normality ranges obtained on an age matched control group and available at the Divieti Laboratory were used.

### 2.3.3 Pedaling test

As the training was performed with a pedaling movement, an evaluation of the performance during cycling is required. The pedaling test sessions was performed at NEARLab.

The test was focused on two main investigation field: the work produced by both the legs and the activation timing of the main muscle involved in the pedaling exercise.

The experimental setup consists of:

1. A motorized cycle-ergometer (Thera-Live<sup>TM</sup>, Medica Medizintechnik GmbH, Germany) customized for the use with individual with stroke [70]. It provides information about the crank angle, the cadence and the crank torque to an external device (such as a PC) with a frequency of 200 Hz. To derive the torque signals, resistance strain gauges were mounted in a Wheatstone full-bridge configuration on both crank arms to measure the right and left bending moments generated during pedaling. According to the theory of elasticity, the strain gauges were placed close to the crank axis, where the strain is greater, two on the upper and two on the lower surface, with the sensing direction aligned to the crank principle dimension. This strain gauges configuration permits both to obtain maximal sensitivity and to compensate radial forces and temperature effect. The torque sensors transmit the signal via a wireless device that provide the sensors conditioning, the data acquisition (with a



12 bit ADC) and transmission to a Micro TxRx Wireless Base Station with Analog Outputs (MicroStrain<sup>©</sup> Inc.) that convert back the digital signal in an analogue one that they acquired with a traditional Data Acquisition (DAQ) board. A schematic representation of the devices is given in Fig. 2.4.

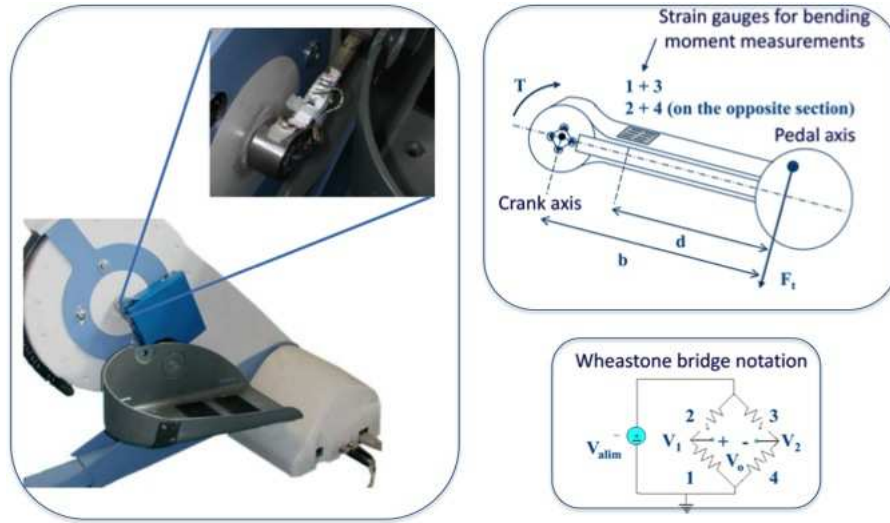


Figure 2.4: Customized cycle ergometer. In the left panel the cycle ergometer and the sensorized crank are shown. In the right upper panel a scheme of the strain gauges mounted on the crank arm is reported. In the right lower panel the electrical scheme of the strain gauges configuration.

To measure the crank angle two optical encoders are used guaranteeing a global resolution of  $4^\circ$ .

Moreover the ergometer is equipped with an engine that, during training, can assist the pedaling guaranteeing a smooth and safe movement. The speed and the resistance of the pedaling movement can be easily adjusted.

2. A multi-channel signal amplifier system for EMG recordings (Porti 32<sup>TM</sup>, TMS International BV, Enschede, The Netherlands). This amplifier is equipped with 32 acquisition channels, among which 12 monopolar, 16 bipolar and 4 channels for auxiliary signals that allow the management of other external sensors. During the present work the bipolar channel were used. The worst noise sources in measuring EMG signal are the movements artifacts between electrode and skin together with network interferences, present in the body as well as in wires. Both the high input impedance and the high common-mode rejection ratio remove the common interfer-

ences at the two electrodes while the cables used have an active shielding pilot by an amplifier which receives the signal from the electrode so to cancel the capacitive coupling between cable and external environment. In order to assure the noise to be minimal during the data transmission towards PC, the signal is transferred via optic fiber cable at a bit rate of 7.168 Mbit/s. From the optic fiber the signal is converted into electrical signal to be transferred to the PC through a USB port.

3. A commercial acquisition board NIDAQ6024E (National Instruments, Texas, USA) that collect information on crank angle and torque sensors.
4. A PC under real time Linux-RTAI. The environment chosen for data acquisition was Scilab/Scicos, an open source software for the numerical calculation that was used to manage a block diagram in order to visualize and memorize data in real time. Once the executable was created, the graphical user interface to RTAI (QRtaiLab) was used to visualize in real time the acquired signal and thus to obtain a visual feedback useful both for the operator and for the patients.

In Fig 2.5 the instrumentation used for pedaling test and the interaction between each block are summarized.

During the test the subjects were seated in front of the ergometer and two ankle foot orthosis (AFOs) were used to stabilize the movement in the sagittal plane, particularly important for the subjects with reduced motor control. The AFOs fixed the ankle joint at 90°. The tests were preceded by the calibration of the torque sensors and by the recording of the crank angle that corresponds to the maximum flexion of the left hip, which depend on the position of the seat and on the antropometric measurement of the subject.

The EMG of 10 muscles of the lower limb (5 for each leg) were recorded with an acquisition rate of 1024 Hz. Single use self-adhesive surface electrodes with a conductive wet gel (Ambu Neuroline 720) were placed on the muscles following the indication of SENIAM [60]. Recording were carried out on the following muscles: rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA), gastrocnemius medialis (GM). Before the experiment a brief (i.e. less than 5 s) maximum voluntary contraction (MVC) in isometric condition was recorded for all the muscles: during a maximum knee extension movement with a resistance that fixed the knee at 90° the MVC of RF and VM have been

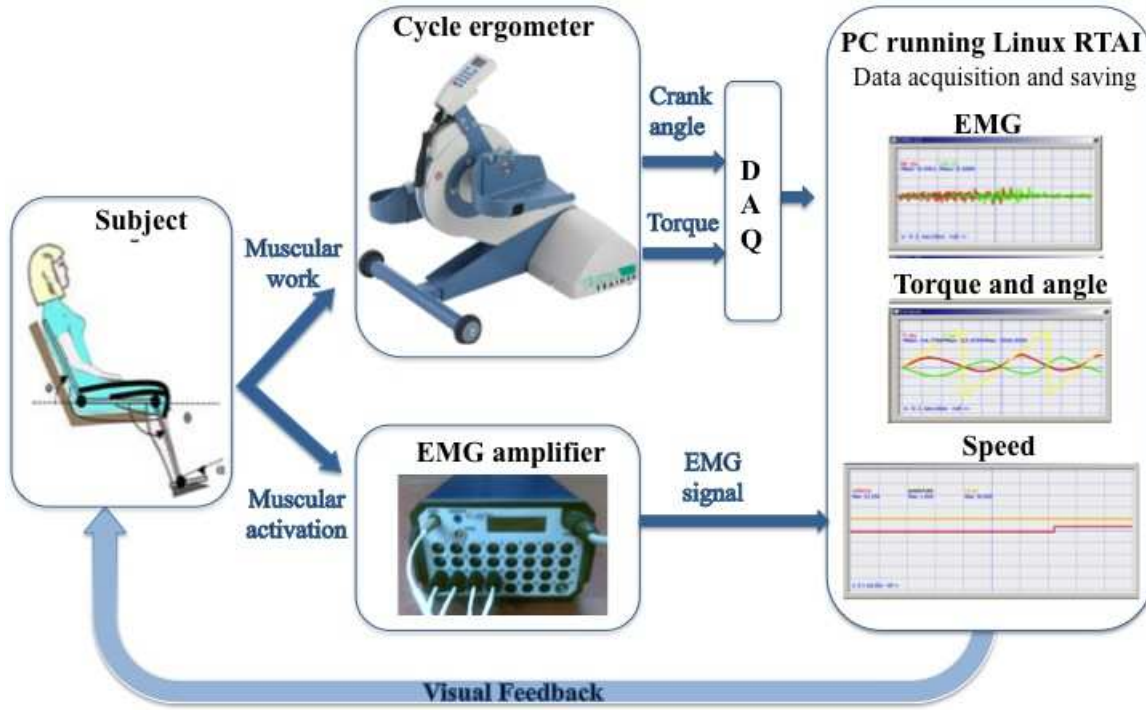


Figure 2.5: Instrumentation used for pedaling test.

obtained, during a maximum knee flexion movement with a resistance on the knee at  $90^\circ$  the MVC of BF has been established and finally with maximum plantar and dorsiflexion movement while the ankle is fixed at  $90^\circ$  the GM and TA respectively are recorded.

In Fig 2.6 a subject while performing the pedaling test is shown.

The overall duration of the test was of 3 minutes. Each patient was asked to perform one minute of passive pedaling during which the ergometer's motor maintained a constant cadence of 30 revolution per minutes (rpm) with no voluntary contribution provided by the subject. Afterwards, the subject was asked to perform two minutes of voluntary pedaling: the operator reduces the speed provided by the motor at 20 rpm and the subjects was asked to reach the speed of 30 rpm pedaling voluntarily. As can be seen in Fig. 2.5, a visual feedback of the actual speed was provided to the subject (red line) as well as the target to be reached and maintained (yellow line). The outcome measures extracted from the pedaling test are the cadence maintained by the subject during the voluntary phase, the mechanical work produced by each leg, the unbalance between them and the muscular activation timing.

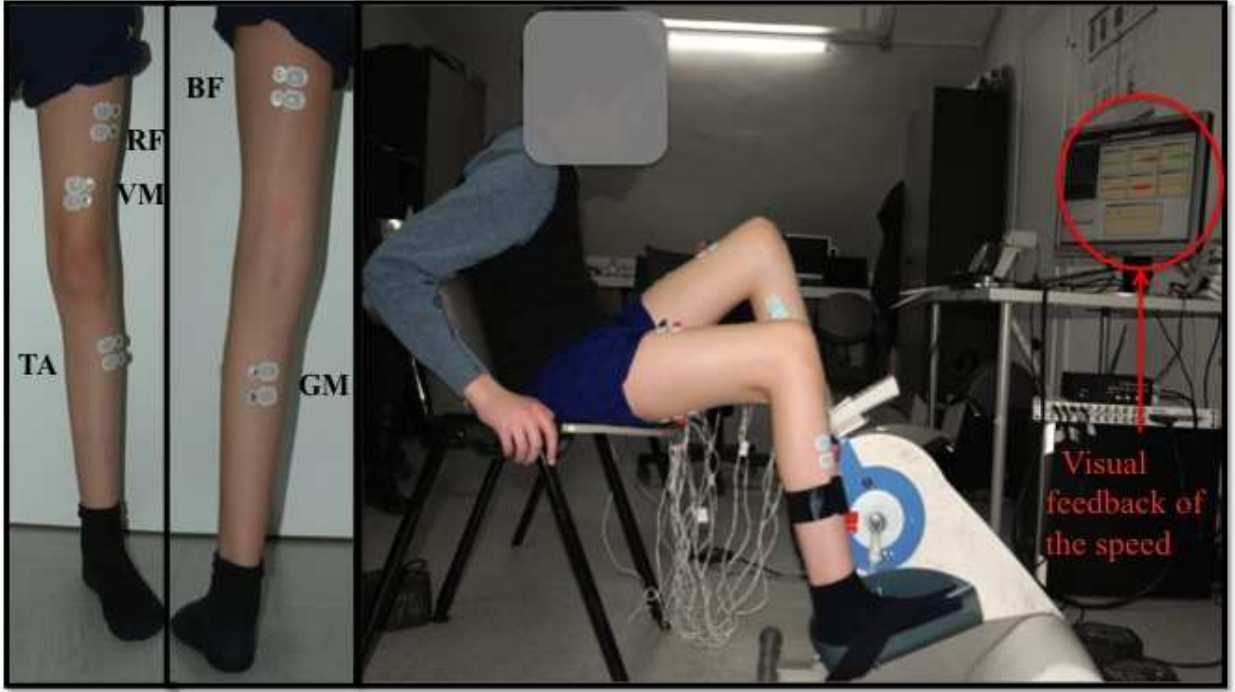


Figure 2.6: Position of the electrodes on rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA), gastrocnemius medialis (GM) and instrumentation used for pedaling test.

### Speed, Work and Unbalance

The ability in maintaining the speed during the voluntary cycling was a first interesting outcome measure of the pedaling test.

One of the most relevant parameter for the evaluation of the motor performance of the subjects was the work produced by each leg during pedaling. The work flow of the algorithm to compute the total active work ( $W$ ), the active work in pushing and pulling ( $W_{PUSH}$  and  $W_{PULL}$ ) and the unbalance ( $U$ ) is shown in Fig. 2.7. For each leg the torque recorded during each revolution of the passive phase of the pedaling was averaged obtaining  $\bar{T}^P$ , mean profiles as function of the crank angle. For each revolution of voluntary pedaling, the voluntary active torque profiles (as function of the crank angle) ( $T^A$ ) were computed by subtracting the passive torques from the measured total torques. Then, the mechanical work values produced by each side was computed as follows:

$$W_{PL} = \int_{0^\circ}^{360^\circ} T_{PL}^A(\theta) d\theta \quad (2.1)$$

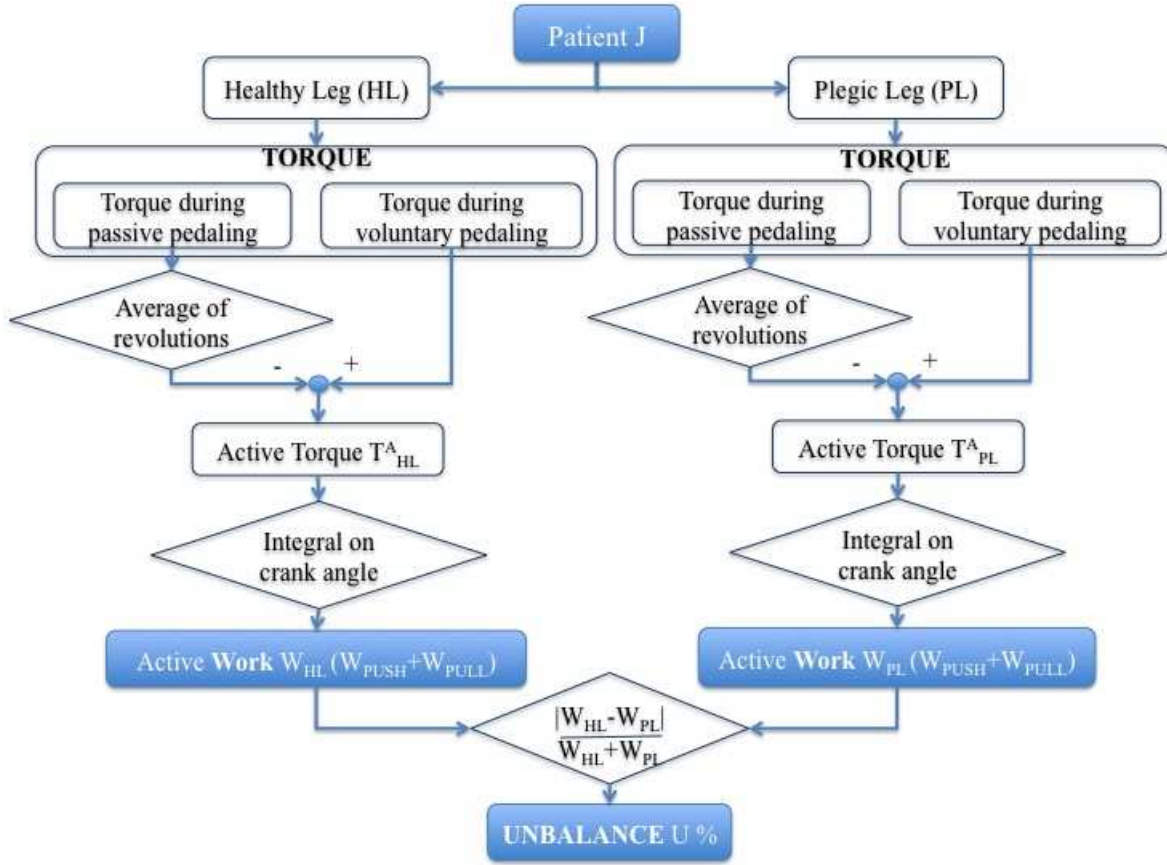


Figure 2.7: Work flow of the algorithm to obtain the work values and the unbalance.

$$W_{HL} = \int_{0^{\circ}}^{360^{\circ}} T_{HL}^A(\theta) d\theta \quad (2.2)$$

where  $T_{PL}^A$  and  $T_{HL}^A$  are respectively the active torque profile of paretic and healthy leg mapped as function of the crank angle  $\theta$ ,  $W_{PL}$  and  $W_{HL}$  are the work produced by the paretic and healthy leg during each revolution of voluntary pedaling.

In order to have a better understanding of the distribution of work during the pedaling kinematic phases, the total work was decomposed into the work produced during knee extension (pushing phase) and that produced during knee flexion (pulling phase). In what follows, we will refer to the work values computed during knee extension by the paretic and healthy leg with the terms  $W_{PUSH}$ . Analogously, the terms  $W_{PULL}$  is referred to the work values produced during knee flexion. The kinematic phases were distinguished by identifying the angular values (dashed black lines in Fig. 2.8) at which the passive torque (green line in Fig. 2.8) was equal to zero. The values of  $W_{PUSH}$  and  $W_{PULL}$  for each leg

was computed as the integral values of the active torque profile in the two identified phases (angular range of positive passive torque indicates  $W_{PUSH}$  while negative passive torque indicates  $W_{PULL}$ ). In Fig.2.8 the measured and active torque during a single revolution as well as the mean passive torque are shown. The symmetry between the work produced by

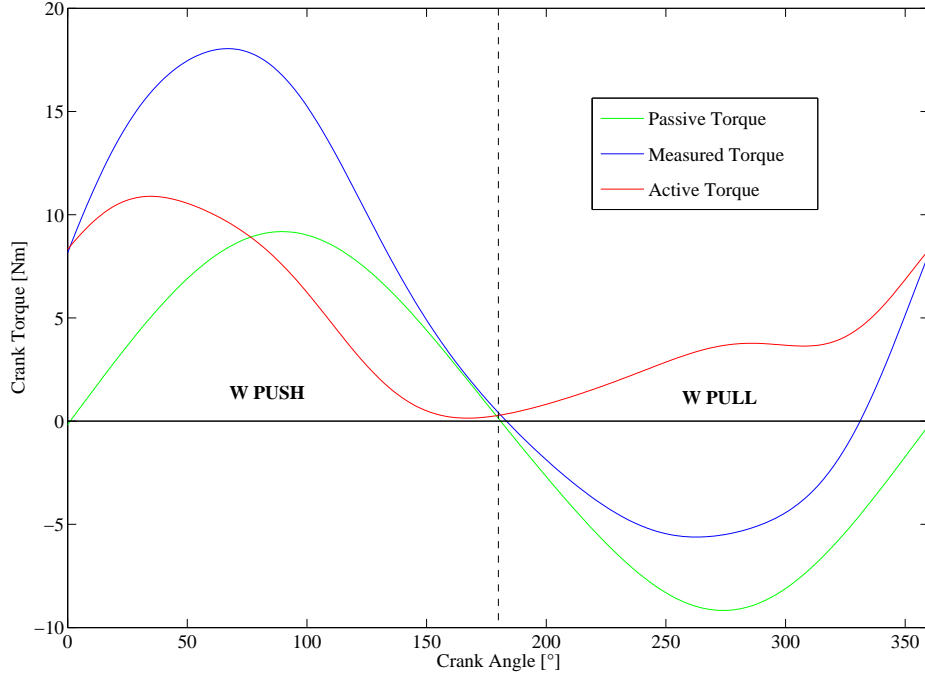


Figure 2.8: Torque data. Green line indicates the passive torque computed as mean of a selection of the revolutions during the passive phase of the test. Blu line shows an example of the measured torque of one of the revolutions during the pedaling phase of the test. Red line corresponds to the active torque computable as difference between the other two. The black dotted lines distinguish the work produced pushing and pulling the pedal.

two legs was assessed by means of an unbalance index ( $U$ ), computed as in Eq. 2.3.

$$U = \frac{|W_{HL} - W_{PL}|}{W_{HL} + W_{PL}} \quad (2.3)$$

$U$  could range from 0% (identical work produced by both legs) to 100% ( $W_{PL}$  equal to zero or negative).

Descriptive statistics was then applied on the data in order to summarize the results of the test. In particular the speed and the work recorded every 20 seconds of acquisition

(about 10 revolutions considering the speed fixed at 30 rpm) were averaged obtaining about 6 values of speed, active work and unbalance for each session. All the data are then presented with the median and inter-quartile values as requested by the statistical analysis described in paragraph 2.4.

### Muscular activation timing

EMG data were used to extract the muscular activation timing during voluntary pedaling. The main steps of the algorithm for the EMG analysis are summarized in Fig. 2.9.

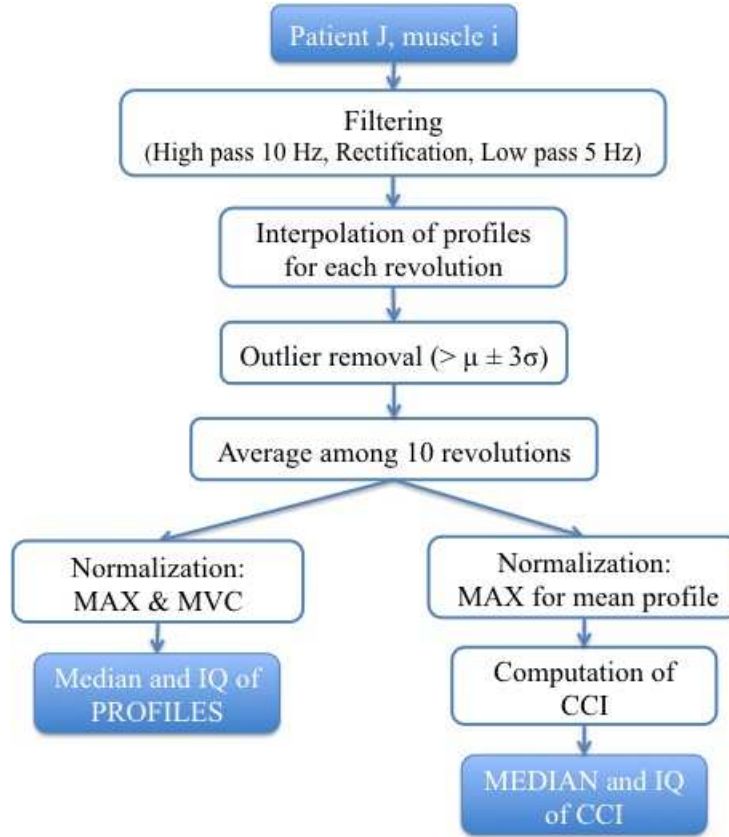


Figure 2.9: Data flow of the algorithm to obtain co-contraction, muscular activation profile and ranges.

The EMG recordings were analyzed according to a standard procedure [56] that can be summarized as follows: firstly the signals were filtered through a 5th order Butterworth high pass filter, with a cut-off frequency of 10 Hz; thereafter, the signal was rectified and low passed filtered by means of a 5th order Butterworth filter, with a cut-off frequency of



5 Hz to obtain a linear envelope. The filtering steps are summarized in Fig. 2.10.

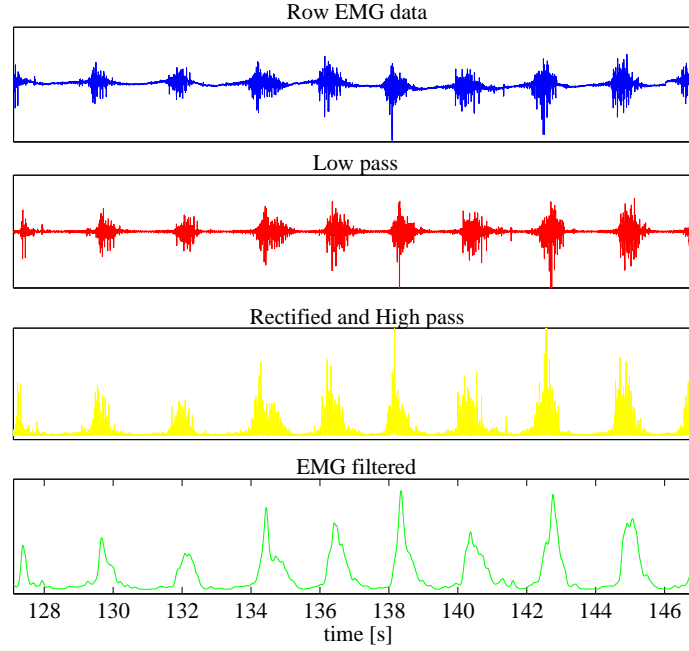


Figure 2.10: Standard procedure applied on the raw EMG data. The upper panel shows the raw data while the last panel represent the EMG envelope.

The next step of the analysis was performed dividing the EMG signal for each revolution and obtaining for each revolution the EMG profile as function of the crank angle. A cubic spline interpolation technique was used to obtain a smooth value of the EMG envelope for each degree of rotation.

Then the algorithm considered only the signal acquired during the voluntary pedaling phase. The revolutions with a profile that differed from the mean profile of more than three standard deviation were considered outliers and removed. Between the remaining revolutions, the average of the profiles acquired every 20 seconds (corresponding to about 10 revolutions if the speed is maintained at 30 rpm) was computed obtaining about 6 mean profiles in 2 minutes of active pedaling.

In order to compare the muscular activity between different muscles and different subjects, the mean EMG profiles were then normalized. Two different techniques were used: the maximal activation value and the Maximum Voluntary Contraction (MVC). Concerning the first one, the maximum value between the 6 mean profiles was chosen as normalization



value. Differently, with the MVC technique the EMG profiles were normalized with respect to the value recorded during an isometric maximum voluntary contraction test. This technique allows to obtain information on the activation level with respect to the maximum achievable. In this way the different sessions can be compared. Because it is not obvious that the EMG values recorded during MVC can be used to represent the maximal neural drive during pedaling [56], this kind of normalization is not always reliable. Thus the MVC normalization was used only for those subjects that during all the four assessment tests were able to perform the MVC test of each muscles above the values obtained during pedaling. The choice of a double approach was made to maintain, if possible, information about the percentage of muscular activation during the exercise.

The 6 normalized profiles achieved were then used to obtain two main outcome measures: the activation profiles and the co-contraction index. The first one was obtained for each muscles as median and inter-quartile ranges of the six mean profiles.

A representation of the procedures and of the results is given by Fig. 2.11. In the example the data is normalized with the maximum. In order to have a better comprehension of the behaviour of the muscles during pedaling, the median profile is studied in comparison with the different kinematic phases of the pedaling as function of the crank angle. In particular the four phases that have been highlighted in a previous study [51] are shown in Tab. 2.6.

I	II	III	IV
0°-140°	140°-170°	170°-324°	324°-360°
Hip extension	Hip extension	Hip flexion	Hip flexion
Knee extension	Knee flexion	Knee flexion	Knee extension

Table 2.6: Crank angle ranges that define the four kinematic phases during pedaling.

These values have to be intended as mean on a healthy population and can be useful to compare the results of the different tests performed by each subject.

The co-contraction between rectus femoris and biceps femoris was assessed as suggested by Trevisi and colleagues [9]. The authors proposed a co-contraction index (*CCI*) was

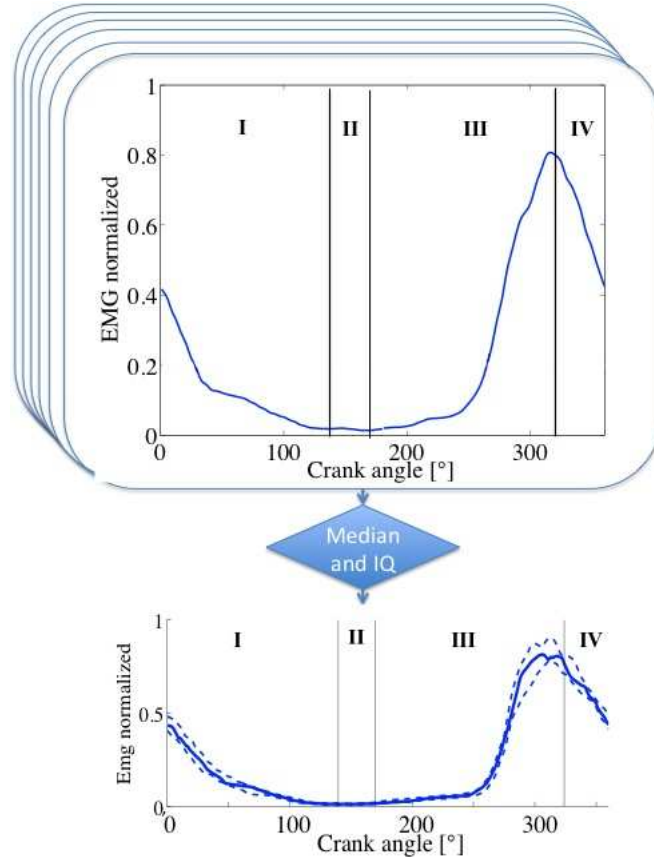


Figure 2.11: Median profile of one single muscle obtained from the algorithm. The inter-quartile ranges are represented as dashed lines.

computed as follows (Eq. 2.4):

$$CCI(j) = \frac{S_{Overlap}(j)}{S_{RF}(j) + S_{VM}(j)} \quad (2.4)$$

where  $S_{RF}(j)$  and  $S_{BF}(j)$  are surfaces areas under the normalized  $j$ -th muscular profile of rectus femoris and biceps femoris muscles respectively while  $S_{Overlap}(j)$  is the overlap area between these two muscles as shown by Fig. 2.12. The CCI is equal to 1 if a complete overlap between the two profiles occurs while is equal to 0 if there is no overlap. Please note that the EMG is normalized to the maximum value of each profile are used to compute the CCI.

Summarizing, the analysis of the pedaling test pursued 5 outcome measures: the speed and the work produced during pedaling, the unbalance between the work produced by healthy and paretic legs, the activation profile (both the shape and the ranges) and the co-

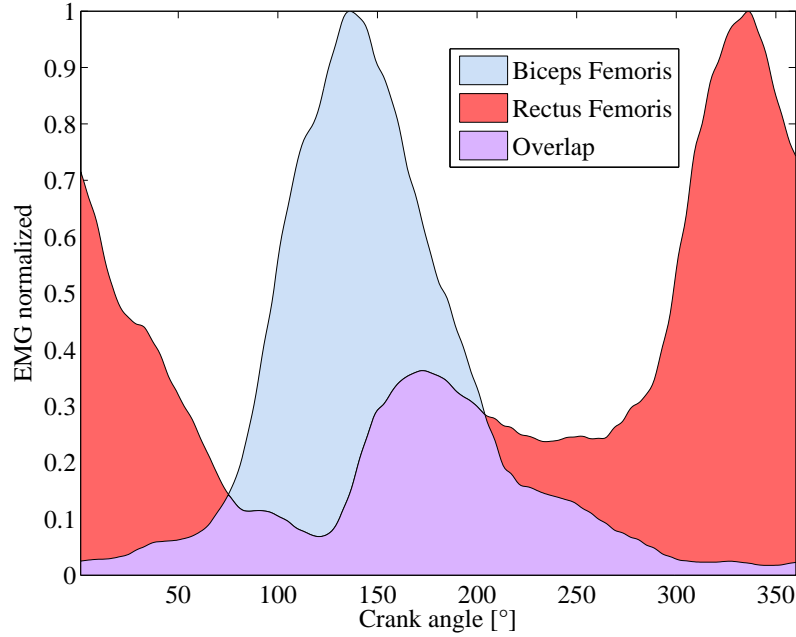


Figure 2.12: Parameters considered for the computation of the CCI.

contraction between couple of agonist-antagonist muscles. In order to obtain the normality ranges for the outcome measures, the pedaling test was performed also on a group of 6 age-matched healthy adolescents that composed the control group (2 men and 4 women with an average age of  $14.3 \pm 1.0$  years, weight  $56.7 \pm 6.6$  kg and height  $163.0 \pm 6.3$  cm).

## 2.4 Statistical analysis

Statistical analysis was performed on gait and pedaling data with IBM SPSS Statistics software in order to assess if any change occurred during the assessment tests. Non-parametric independent sample statistic tests were considered as low number of data with no information about their distribution was compared. The dependent variable chosen for the statistical analysis of the pedaling test included the work, the unbalance, and the co-contraction index. Concerning the gait analysis the tempo-spatial parameters were considered as well as some punctual measurement of kinematic and kinetic.

No statistical analysis with an healthy control group was performed for the gait analysis because only mean and standard deviation data were available.

Differently for the pedaling test a Mann-Whitney U test was performed in order to compare the differences between each subject and the healthy subjects group at the four different time points. To assess the effect of time for each subject (as the four independent variable oPRE, PRE, POST and FU were considered) a Kruskal-Wallis test was used for both the pedaling and the gait analysis. If after each Kruskal-Wallis test a significant difference was found ( $P < 0.05$ ), a post-hoc analysis was performed comparing pairs of tests (oPRE vs PRE, oPRE vs POST, oPRE vs FU, PRE vs POST, PRE vs FU, POST vs FU).

## Chapter 3

# Results and Discussion

Six male patients were recruited but two of them withdrew with the study during the second week of the intervention as the effort required by the study was not compatible with their every day activities.

Details about the four subjects that concluded the study (S1, S2, S3 and S4 in the following) are reported in Tab. 3.1. As told in paragraph 2.2 the intervention was customized

	<b>Age</b> (years)	<b>Gender</b> (M/F)	<b>Height</b> [cm]	<b>Weight</b> [kg]	<b>Hemiparesis</b> side (R/L)	<b>Etiology</b>
<b>S1</b>	15	M	165	45	R	CP
<b>S2</b>	14	M	170	90	R	CP
<b>S3</b>	12	M	161	46	L	CP
<b>S4</b>	17	M	175	63	R	Ischemic stroke

*Table 3.1: Participants' details at baseline*

and for each subject the amplitude of the current values and the resistance to the voluntary pedaling were differently set during the first three sessions of training. A summary of the final values obtained is shown in Fig. 3.2.

The four patients underwent four assessment sessions (observational PRE or oPRE, PRE, POST and FU) composed by a clinical evaluation performed at Institute Besta, a gait analysis at Divieti Laboratory and a pedaling test carried out at NEARLab.

	<b>S1</b>		<b>S2</b>		<b>S3</b>		<b>S4</b>	
	$P_{Leg}$	$H_{Leg}$	$P_{Leg}$	$H_{Leg}$	$P_{Leg}$	$H_{Leg}$	$P_{Leg}$	$H_{Leg}$
Quadriceps [mA]	20	15	30	25	20	15	20	30
Gluteus maximus [mA]	15	20	30	30	15	15	20	15
Hamstring [mA]	25	20	30	30	25	20	30	35
Tibialis anterior [mA]	30	25	35	40	25	25	25	30
Resistance	8/20		14/20		10/20		7/20	

Table 3.2: Electrical current values and resistance customized for the four subjects' training.  $P_{Leg}$  indicate the Paretic Leg values and  $H_{Leg}$  the Healthy Leg values.

No group analysis was performed as the sample size was too small thus the results are presented singularly.

The normality ranges of the gait analysis parameters were obtained during previous studies performed at the Divieti Laboratory. Therefore, sine individual data were not available, a statistical comparison between patients and healthy subjects was not possible for the gait parameters. Concerning the pedaling test trials on an age-matched healthy control group were carried out.

### 3.1 Control Group for pedaling assessment

An age-matched healthy control group underwent the pedaling test in order to obtain the normality ranges. Details about the six subjects are shown in Tab 3.3. The ability in maintaining the speed required during the exercise can be an index of the performance of the test and the variations can be an index of the attention focused on the execution of the exercise. The median value obtained by the control group (CG) is equal to 30.64 rpm with interquartile ranges of 0.20 rpm.

Another parameter that was considered was the work produced by each leg during pedaling. It is well known that since the first years of life healthy subjects have a dominant limb. During the pedaling test the dominance of the healthy subjects was identified in

	Age (years)	Gender (M/F)	Height [cm]	Weight [kg]	Dominant side (R/L)
<b>C1</b>	15	F	158	56	R
<b>C2</b>	15	F	159	54	L
<b>C3</b>	15	F	171	55	L
<b>C4</b>	15	F	155	45	R
<b>C5</b>	13	M	165	65	R
<b>C6</b>	13	M	170	63	R

Table 3.3: Control group' details.

order to compare the paretic limb of the patients with the non-dominant leg of the CG. The dominance was highlighted in the non-symmetrical production of work during pedaling. The value obtained are summarized in Fig. 3.1. The total work produced by non

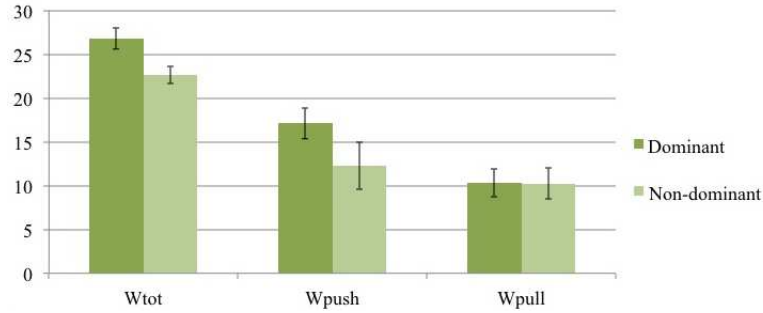


Figure 3.1: Median work for CG. The overall work is represented as well as the work produced in pushing and pulling phases. Median values and inter-quartile (error bars) ranges are shown for both dominant and non-dominant leg.

dominant leg was minor due to a decreased pushing work during pedaling. The percentage of the median unbalance (U) obtained for the CG was equal to 10.3% with an inter-quartile (IQ) ranges equal to 6.0%.

Concerning the EMG activation the results achieved for the five muscles of both dominant and not dominant leg are shown in Fig. 3.2 and Fig. 3.3.

The two figures show the profiles obtained with the two different methods of normalization

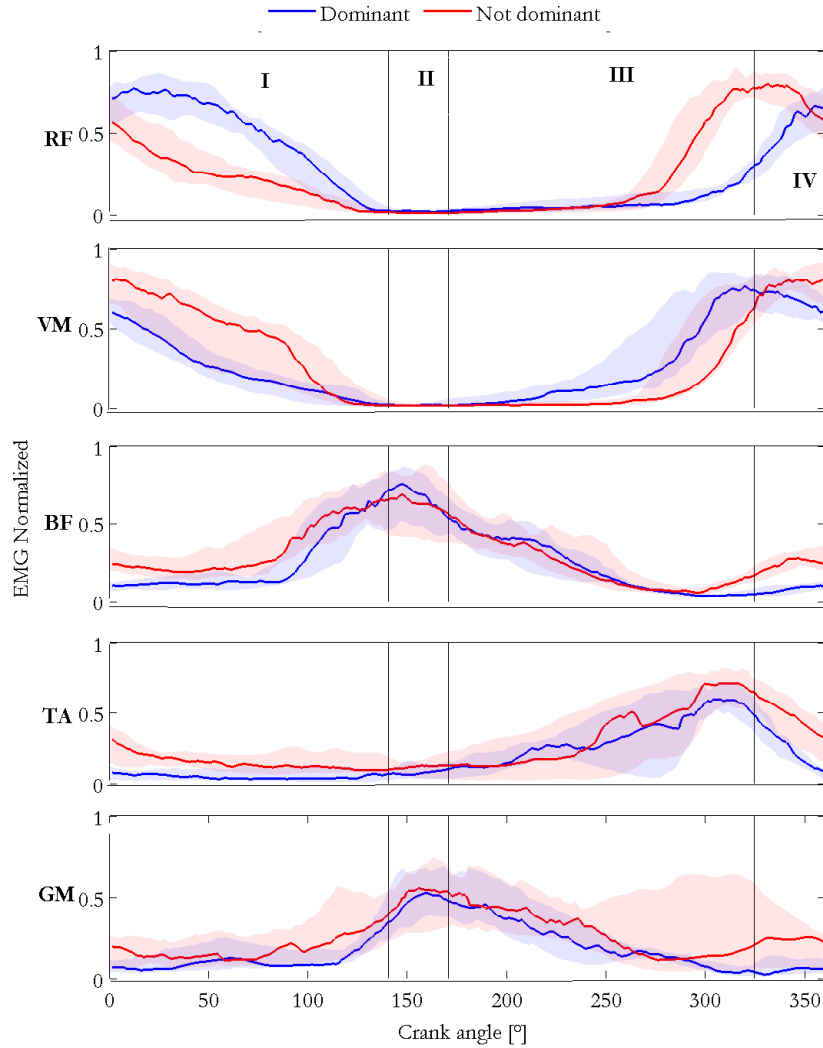


Figure 3.2: EMG profiles with respect to crank angle obtained normalizing with the maximum activation value of the profiles. Median and interquartile ranges are shown as bold line and coloured area respectively. Kinematic phases are shown: I hip and knee extension, hip extension and knee flexion, III hip and knee flexion, IV hip flexion and knee extension.

described in paragraph 2.3.3 and represent EMG profiles with respect to the kinematic phases of the pedaling (I-VI). Each EMG profile was plotted as function of the crank angle and  $0^\circ$  represents, for each leg, the maximum flexion of the hip.

It can be noticed that the profiles of the rectus femoris (RF) and the vastus medialis (VM)



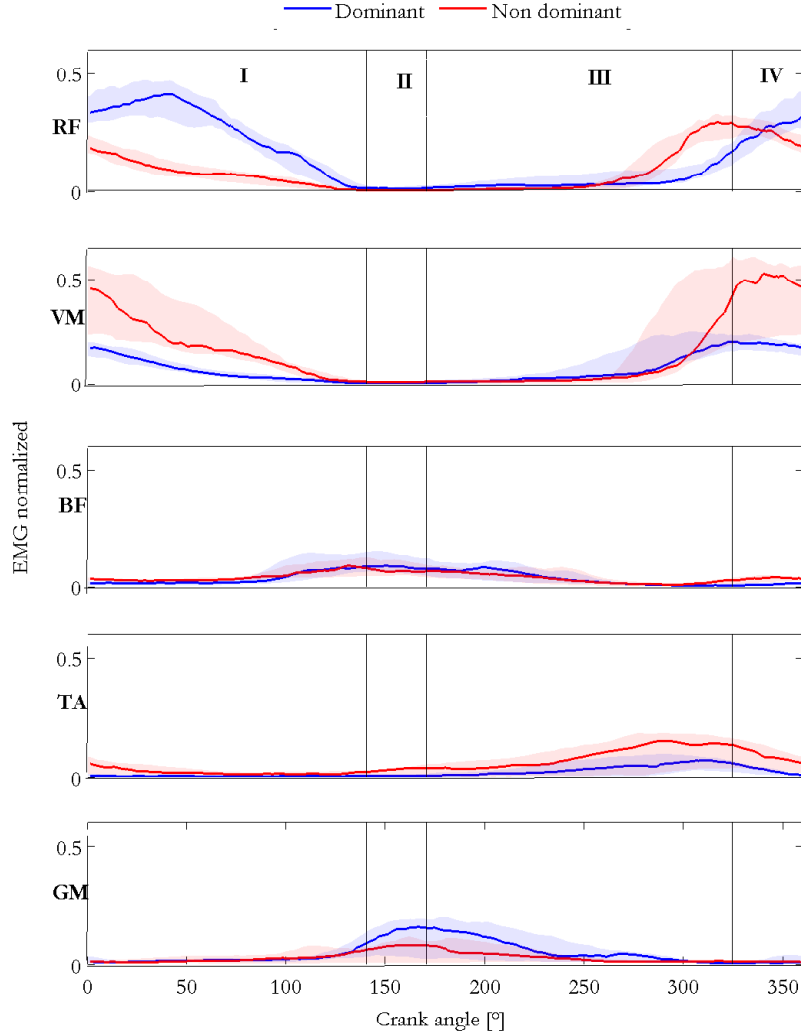


Figure 3.3: EMG profiles with respect to crank angle obtained normalizing with respect to the activation value obtained during the maximum voluntary contraction (MVC) test. Median and interquartile ranges are shown as bold line and coloured area respectively. Kinematic phases are shown: I hip and knee extension, hip extension and knee flexion, III hip and knee flexion, IV hip flexion and knee extension.

differ for dominant and not dominant leg although the subjects were healthy. As expected, these two muscles were active mainly during the knee extension (VI-I phases). The RF was also active in hip flexion (III phase) but this effect is reduced during pedaling as the controlateral leg compensates the movement. Differently from our results, in literature [56]

the activation timing of this couple of muscles during pedaling usually showed that the RF is phase-advanced with respect to the VM.

The biceps femoris contributed during hip extension and knee flexion, located between the phases I and the II. The activation was low with respect to the maximum voluntary contraction of that muscle (about the 10% of the MVC as can be seen in Fig. 3.3) and moreover it presents a greater inter-variability between the subjects. Finally the tibialis anterior (TA) and the gastrocnemius medialis (GM) had a little activation with respect to their MVC (14% and 15% respectively) and a great variability between subjects. That was probably caused by the fact that the cycle-ergometer was equipped with an ankle foot orthoses (AFO) that fixed the ankle angle at  $90^\circ$  decreasing the muscular contribution of TA and GM to the pedaling. Their timing of activation was correct: GM was active during knee flexion (II and III phases, delayed with respect to BF involved also in hip extension of II phase) while TA was involved in ankle dorsiflexion during III and VI phases.

Moreover, this low levels of activation are supported by literature. In fact a review by Hug and colleagues [56] showed that the quadriceps is the muscular group more active during pedaling.

Finally the co-contraction between the couple of agonist-antagonist composed by rectus femoris and biceps femoris was studied. The results obtained for the healthy subjects were coherent with what obtained by Trevisi and colleagues (see 2.3.3 for further information) as summarized in Tab. 3.4.

	Median	I quartile	II quartile	IQ ranges
<b>Dominant leg</b>	0.35	0.18	0.42	0.23
<b>Not dominant leg</b>	0.34	0.27	0.42	0.15

*Table 3.4: Co-contraction index for dominant and not dominant legs of control group.*

It can be noticed that the variability among subjects was high.

## 3.2 Subject 1

The first subject (S1) was a 15 years old male affected by cerebral palsy. Detailed information about the clinical evaluation at baseline as well as after the treatment during both short and long term assessment tests are presented in Tab. 3.5.

Clinical Scale	oPRE	PRE	POST	FU	Ranges (Mild-Severe)
Winter Scale	I	I	I	I	I - IV
GMFM	99.15%	98.90%	100%	100%	100% - 0%
Boyd Test	3/4	3/4	3/4	3/4	4 - 0
OGS	17/21	17/21	17/21	17/21	22 - -2
Ashworth Scale	2/0	2/0	2/0	2/0	0 - 4

Table 3.5: Clinical assessment for subject 1. The classification with the Winter scale and the results of GMFM, Boyd test, Ashworth scale and OGS are presented as paretic/healthy leg

It can be noticed that the subject was affected by a slight impairment at baseline. The Boys test showed some impairment in the distal voluntary control, maintained over time. Only the gross motor function of the patient, assessed by the GMFM, had a slight improvement (about 1%) while all the other parameters remain unvaried. In particular the Winter scale and the OGS suggested that no evident changes occurred in locomotion ability while the Ashworth scale showed that the level of spasticity was maintained.

### 3.2.1 Gait analysis

The temporal-spatial gait parameters are summarized in Tab. 3.6. The subject was able to walk at a speed just below the normality range. No significant difference was obtained over time ( $p > 0.05$ ). A study conducted by Tilson and colleagues [11] considered walking speed  $\geq 0.8$  m/s characterizes people without substantial limitation, thus the results confirmed slight impairment highlighted by the clinical assessment.

Concerning the step length, both paretic and healthy leg were maintained within the normality ranges (except for the healthy limb at FU). A significant difference was highlighted between PRE and FU tests. The symmetry index was just below 1 and was maintained

	oPRE	PRE	POST	FU	CG	P-value	Post-Hoc
V [m/s]	1.02 (0.02)	1.07 (0.05)	1.10 (0.05)	1.11 (0.15)	1.31 (0.60)	0.125	
$L_{PL}$ [mm]	555.0 (4.0)	574.3 (7.5)	587.5 (24.0)	598.0 (25.1)	559.8 (48.0)	<b>0.037</b>	PRE vs FU p=0.024
$L_{HL}$ [mm]	570.0 (6.5)	585.1 (2.0)	587.3 (6.3)	611.0 (71.8)	559.4 (45.1)	<b>0.003</b>	PRE vs FU p=0.001
SI [ ]	0.97 (0.06)	0.97 (0.01)	0.98 (0.04)	0.96 (0.05)	1.03 (0.23)	0.589	

Table 3.6: Comparison of temporal-spatial parameters between oPRE, PRE, POST and FU. The values are represented as median (inter-quartile ranges) obtained during the different repetitions of each gait assessment. The Kruskal-Wallis statistical difference is shown as bold number.

over time, suggesting that the step length was quite symmetrical.

The kinematic analysis (Fig. 3.4) allowed us to highlight an increased range of motion (ROM) concerning the dorsi-plantar flexion of the ankle during swing phase.

The median results obtained during repetitions of each of the four assessment tests are represented as coloured line, red and magenta for the tests before the training and blu and ciano for the POST and FU tests. The green line showed the trend of the angle for healthy population (the coloured area is the inter-quartile range). In particular the range of motion of both paretic and healthy leg were reduced in plantarflexion (angle<0) and in dorsiflexion (angle>0) during the swing phase of oPRE and PRE tests. Some improvement was shown after the treatment restoring the functional ROM of healthy side in POST test and of paretic side in POST and FU. Moreover the plantar flexion angle was improved after the treatment in POST test for both legs and maintained at FU for the paretic leg. The statistical analysis showed significant difference of ROM for paretic legs (p=0.019, post hoc: PRE vs POST p=0.034).

The analysis of the kinetic during gait reveals interesting results concerning the ankle power. In particular the functional propulsive ankle power during push off phase of the

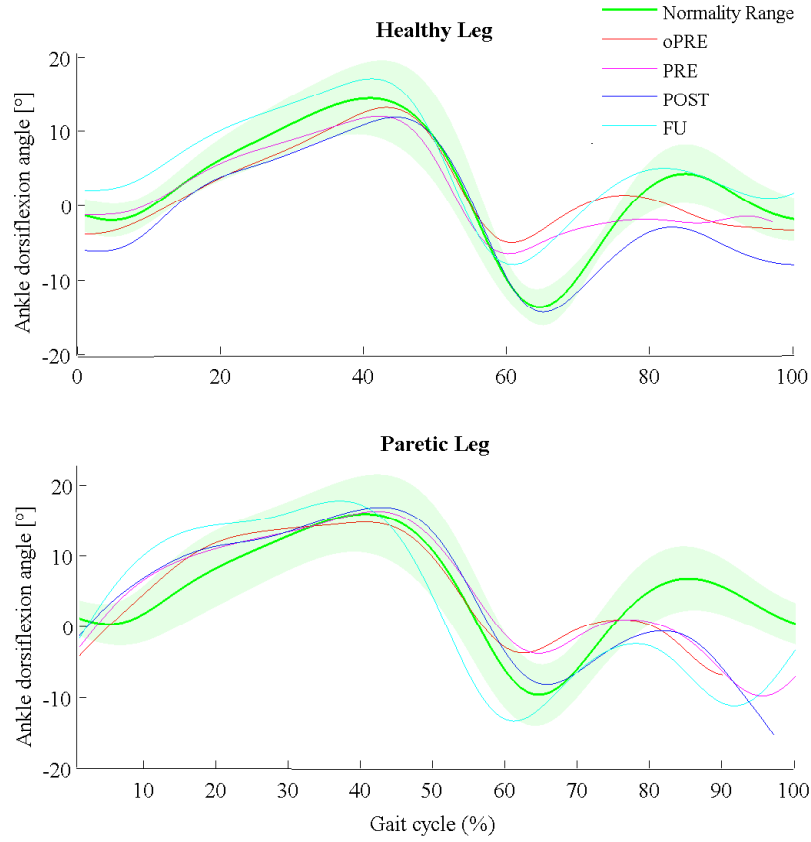


Figure 3.4: Angle of ankle dorsi (angle  $> 0$ ) and plantar (angle  $< 0$ ) flexion over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

gait cycle was improved after the treatment as can be observed in Fig. 3.5.

The statistical analysis showed a significant difference in terms of the maximum power of the paretic leg ( $p=0.028$ ), in particular between PRE versus POST ( $p=0.022$ ) and FU ( $p=0.012$ ) and PRE versus POST ( $p=0.032$ ). An improvement of about 25% peak to peak was shown between PRE and POST. The ankle power is computed from the ankle moment and the ankle angular speed (that is in relation with the the angular coefficient of the range of motion that is known from the kinematic analysis of the movement). As the ankle moment did not change over time (data not reported), the augmented ankle power for S1 can be attributed to changes in angular speed (angular coefficient in Fig. 3.4).

The analysis of the ground reaction force showed some changes in the vertical force as it

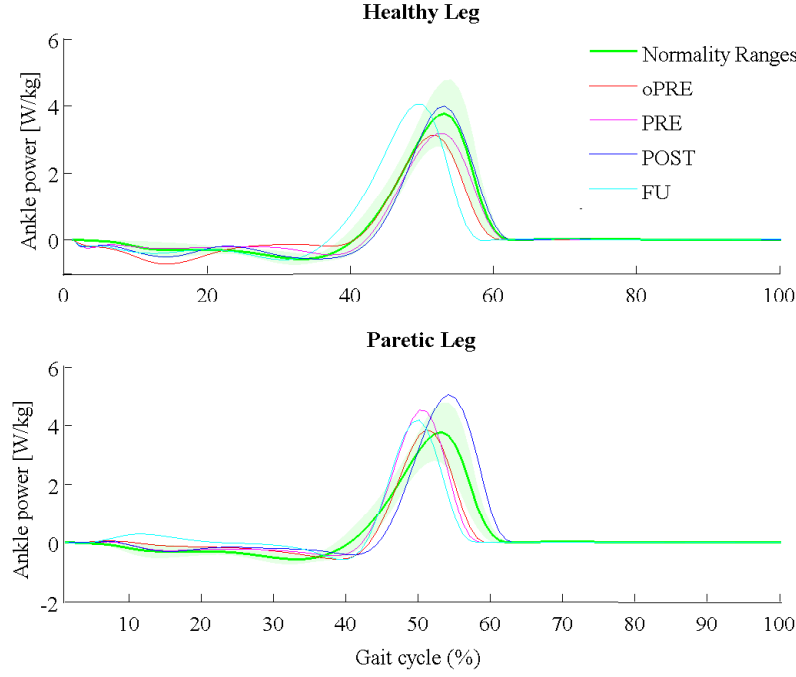


Figure 3.5: Ankle power over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

can be noticed in Fig. 3.6.

In particular the values at baseline were within the normality ranges but an increased force was produced during load support and pushing off phases at FU, in particular for the paretic leg.

Therefore, although the reduced deviation in gait parameters, slight improvement in some gait parameters was achieved by the first subject after training.

### 3.2.2 Pedaling test

The results presented for the pedaling test of S1 are not complete as the instrumentation was not available at the moment of the assessment test just before the FES training, thus results about PRE session are marked as NA in the following.

The ability in maintaining the speed during pedaling, can be considered as a first index of the performance of the subjects during the test. In Tab. 3.7 the median and IQ values of the speed for each assessment test are reported and compared to the median and IQ values of the control group speed. In the test performed during the first assessment (oPRE) the

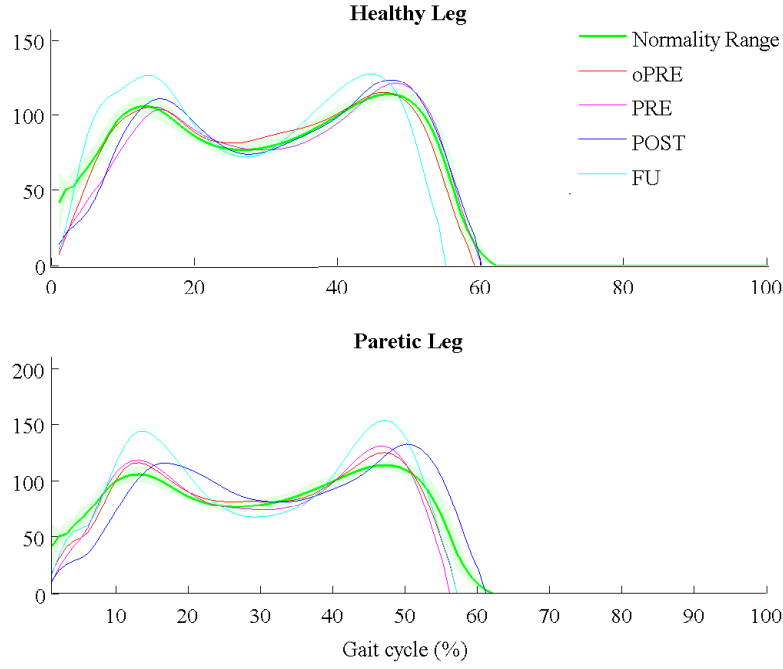


Figure 3.6: Vertical force over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

	oPRE	PRE	POST	FU	CG
V [rpm]	27.2 (1.47)	NA	30.3 (0.9)	30.1 (1.1)	30.6 (0.2)

Table 3.7: Comparison of velocity during pedaling within oPRE, PRE, POST and FU. The values are represented as median (inter-quartile ranges) obtained from the revolutions during each session.

speed requested to the subject (30 rpm) was not perfectly maintained while during POST and FU tests the subject was able to maintain the speed as the control group did.

Concerning the work produced by healthy and paretic leg the results are shown in Fig. 3.7.

For both paretic and healthy legs the overall work  $W_{TOT}$  was within the normality ranges. Analysing the production of the work, it can be observed that the paretic leg produced a bigger amount of work by pushing the pedal ( $W_{PUSH}$ ) with respect to the healthy subjects. After the treatment the work was correctly decreased in pushing, maintaining the overall production of work as the work in pulling was increased. The statistical analysis showed

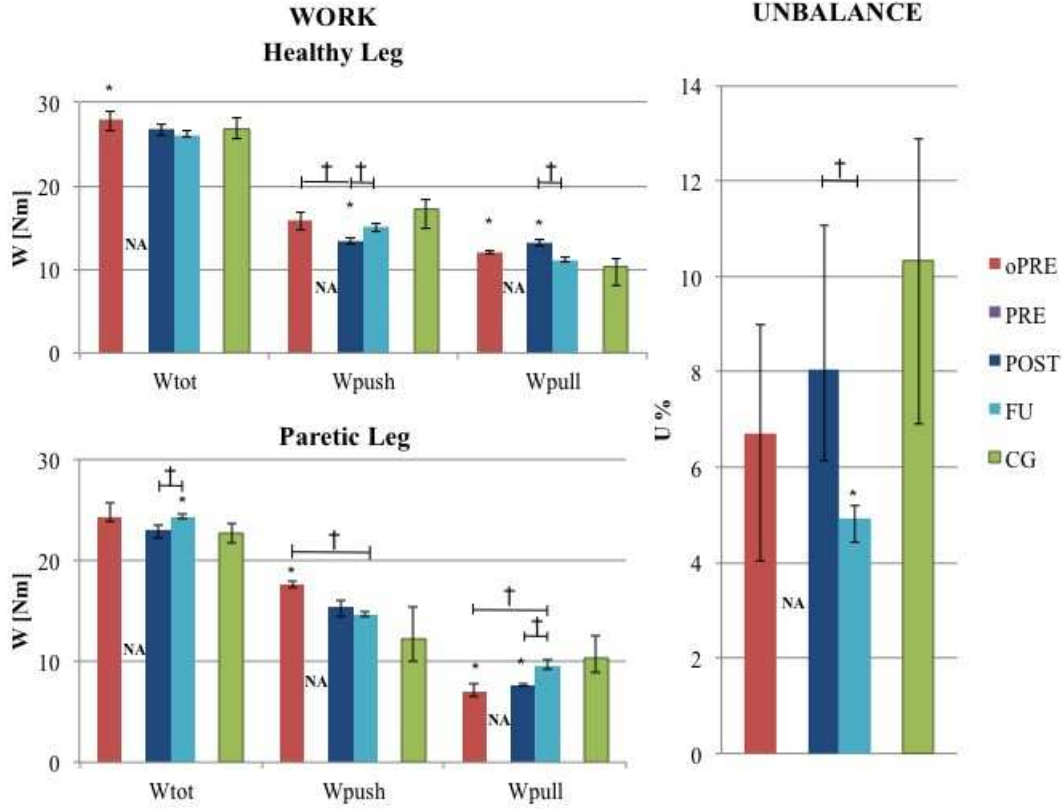


Figure 3.7: Work and unbalance  $U$  over time (coloured scale). The median and inter-quartile ranges (error bars) of the total work produced while the two legs as well as the pushing and pulling work are shown. The right panel represents the unbalance between the overall work of the two legs. † indicates significant difference ( $p < 0.05$ ) obtained with post-hoc analysis of Kruskal-Wallis test while \* indicates a significant difference with the control group (CG).

that both  $W_{PUSH}$  and  $W_{PULL}$  of the paretic leg were significantly different between PRE and FU tests. Moreover also the healthy leg showed significant difference in  $W_{PUSH}$  and  $W_{PULL}$  as it can be observed in Fig. 3.7. In terms of unbalance ( $U$ ) between the overall work produced by the two legs a normal values was obtained at baseline and maintained over time, as shown by results in Fig.3.7. The FU was significantly ( $p < 0.01$ ) decreased with respect to the normality range resulting in a very symmetric movement.

Concerning the EMG signals acquired during the pedaling test, the profiles of each muscle during the four assessment tests were analyzed in comparison to the healthy subjects' profiles. S1 was not able to achieve his maximum contraction during the MVC test. In



particular the level of activation of the paretic vastus medialis during MVC was below the activation obtained during the pedaling. Thus the normalization with the maximum activation value obtained during pedaling was preferred. Fig. 3.8 and 3.9 show the profiles of healthy and paretic leg respectively. Please note that the interquartile ranges obtained for the patient tests are not shown in order to have a clearer representation.

The activation of the healthy rectus femoris (RF) was slightly postponed both in onset and offset during oPRE while the POST test showed a profile within the control group ranges. The FU profile did not maintain the improvement since it was very similar to the oPRE. The vastus medialis (VM) had a slightly postponed activation at onset while was correctly activated at POST and FU. The timing of activation of the couple RF-VM suggests that the flexion of the hip (III and IV phase) was not achieved by the RF that intervened mainly when the knee extension started (IV phase).

The biceps femoris (BF) was characterized by a postponed maximum that was correctly anticipated after training but not maintained at FU. However the POST test presented a second activation not present in the control group.

Concerning the tibialis anterior (TA) the maximum peak of POST and FU tests was characterized by a correct timing while the oPRE test showed a postponed peak with a wide activation profile. The gastrocnemius medialis (GM) was characterized by a similar behaviour between oPRE and POST while the signal at FU had a very high variability. In fact, confirming what observed on healthy subjects, the interquartile ranges (not shown) showed that the signal of TA and GM was very spanned and thus with few reliability. That was probably caused by a very low level of activation, as occurred in the control group.

The paretic leg was characterized by slight changes over time in the profiles of RF, VM and BF. In particular, both RF and VM showed a postponed activation peak during oPRE test, correctly anticipated during POST test but postponed again at FU. Moreover the RF had a reduced range of activation in all the tests. As the RF intervened between III and IV phases and the VM was active during the whole phase I, the flexion of the knee was mainly performed by the VM.

The BF showed a correct activation during both PRE and POST tests while the profile during FU was characterized by an early onset in I phase (hip and knee extension).

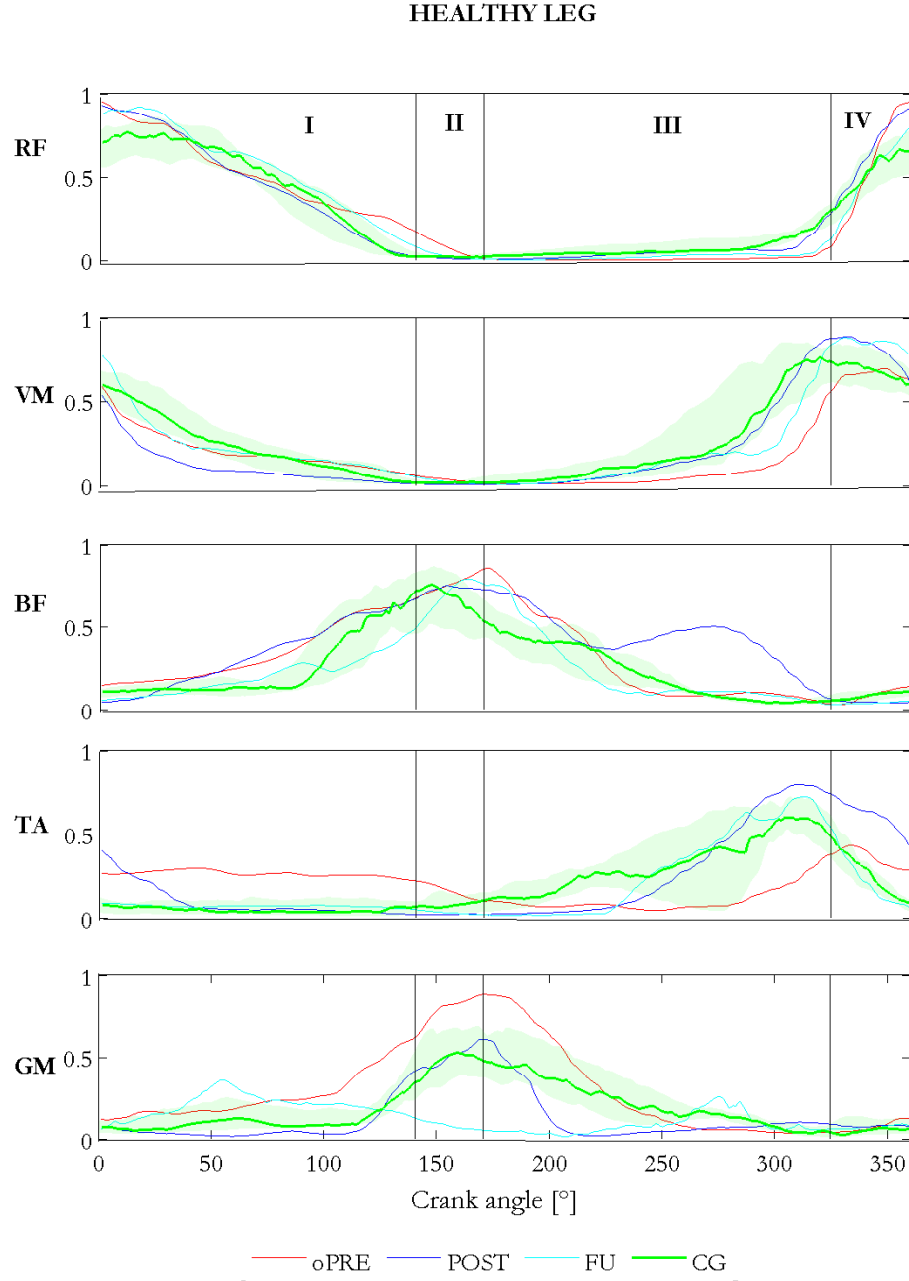


Figure 3.8: Median EMG profiles with respect to the crank angle of the five muscles for S1 healthy leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.

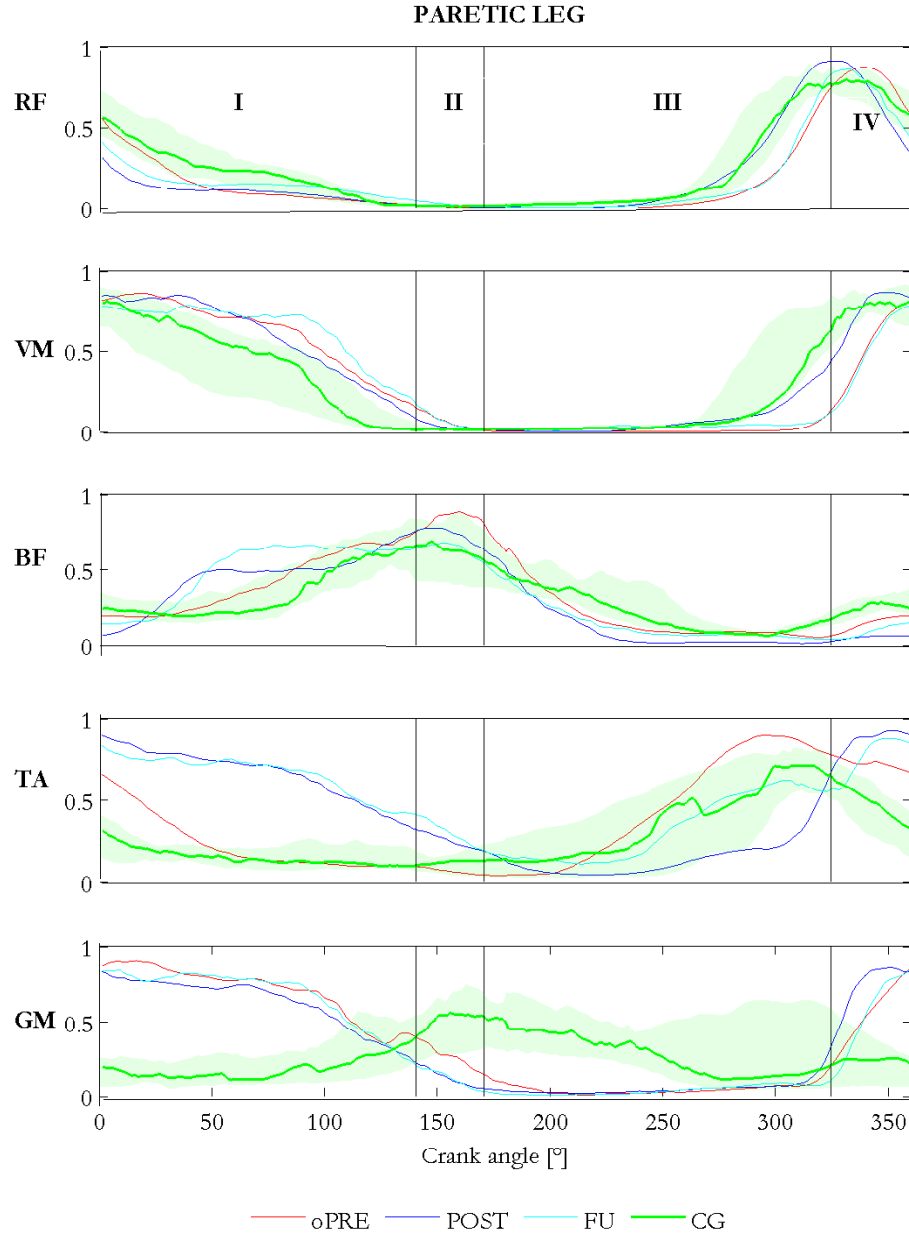


Figure 3.9: Median EMG profiles with respect to the crank angle of the five muscles for S1 paretic leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively

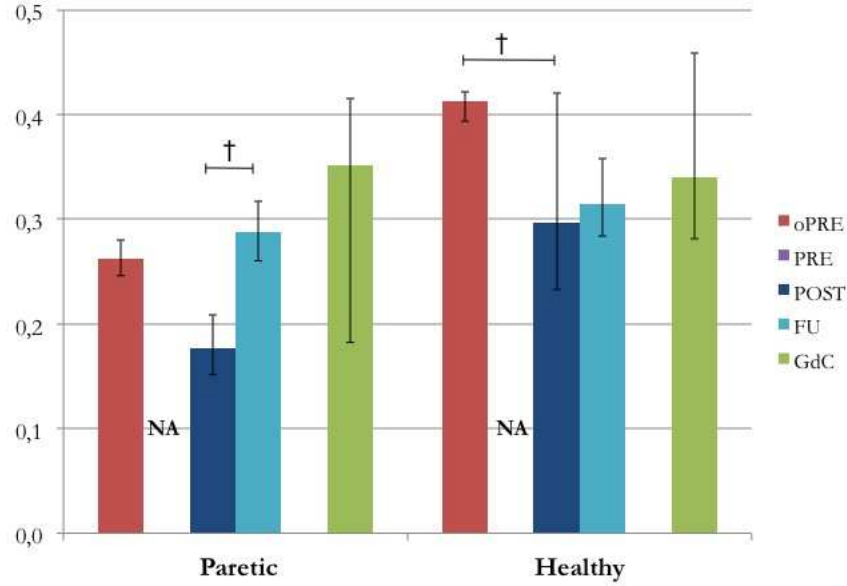


Figure 3.10: Co-contraction index of paretic and healthy legs of S1 is shown. † indicates statistical difference over time while \* between each test and the control group.

The profile of TA was correctly timed at PRE but the offset was postponed in POST and FU. Finally GM showed a completely opposite activation strategy with respect to the healthy subjects, maintained over time.

Summarizing, the results of RF and VM of both healthy and paretic leg showed slight deviation from the CG profiles at baseline and was correctly changed over time. The BF maintained a correct activation peak while the TA and GM of paretic leg were not well-timed and did not improved over time.

From activation profiles of RF and VM, the co-contraction between rectus femoris and vastus medialis was also studied. Data are reported in Fig. 3.10. The patient showed no deviation at baseline. As can be observed some changes over sessions was obtained (POST-FU for paretic leg and oPRE-POST for healthy leg) but these differences were maintained within the control group as no statistical difference was found between each session and the normality ranges.

### 3.3 Subject 2

Subject 2 (S2) was 14 years old patient affected by cerebral palsy that produced an impaired motor control of the right side of the body.

The clinical assessments over time are summarized in Tab. 3.8. Only a slight disability

Clinical Scale	oPRE	PRE	POST	FU	Ranges (Mild-Severe)
Winter Scale	I	I	I	I	I - IV
GMFM	99.21%	99,21%	99,21%	99,21%	100% - 0%
Boyd Test	3/4	3/4	3/4	3/4	4 - 0
OGS	16/21	16/21	16/21	16/21	22 - -2
Ashworth Scale	1/0	1/0	1/0	1/0	0 - 4

Table 3.8: Clinical assessment over time for Subject 2. The classification with the Winter scale and the results of GMFM, Boyd test, Ashworth scale and OGS are presented as paretic/healthy limb.

was pointed out at baseline and no changes occurred after the treatment. In particular a good distal control (Boyd test) was shown as the flexion of the foot was followed only by a light knee flexion at the end of the range of motion. A mild increased muscular tone (Ashworth scale) was assessed in all the tests. The Winter scale score and the OGS also reflected a good locomotion ability.

#### 3.3.1 Gait analysis

The gait temporal-spatial parameters are summarized in Tab. 3.9.

The walking mean velocity showed no statistical difference over time and was maintained just below the gait speed of the control group.

The step length of the paretic limb had a value within the normality ranges already at baseline that was maintained over time. Also the healthy step length was within the normality ranges already at PRE but it changed over time showing a significant difference between PRE and FU tests ( $p=0.014$ ). The SI was maintained within the normality ranges but significantly changed over time. In fact a progressive reduction of  $L_{HL}$  produced a

	oPRE	PRE	POST	FU	CG	P-value	Post-Hoc
V [m/s]	1.06 (0.04)	1.01 (0.07)	0.96 (0.10)	0.92 (0.04)	1.31 (0.60)	0.053	
$L_{PL}$ [mm]	560.0 (9.0)	533.3 (38.5)	554.5 (13.0)	549.0 (24.1)	559.8 (48.0)	0.121	
$L_{HL}$ [mm]	589.0 (16.5)	603.0 (52.0)	600.3 (23.3)	527.0 (10.8)	559.4 (45.1)	<b>0.012</b>	PRE vs FU p=0.014
SI [ ]	0.91 (0.08)	0.87 (0.03)	0.92 (0.05)	1.07 (0.02)	1.03 (0.23)	<b>0.005</b>	PRE vs FU p=0.002

Table 3.9: Comparison of temporal-spatial parameters between oPRE, PRE, POST and FU. The values are represented as median (inter-quartile range) obtained during the different repetitions of each gait assessment. The Kruskal-Wallis statistical difference is shown as bold number and the post-hoc results are summarized.

increasing symmetry over time.

The kinematic analysis of the locomotion revealed more relevant distal deviation. A reduced range of motion was observed in dorsi-plantar flexion of the ankle for both healthy and paretic limb (see Fig. 3.11).

The plantar flexion (angle<0) was particularly impaired at toe off and swing phase. Concerning the paretic limb, a significant improvement not attributable to the training was observed between the minimum plantar-flexion angle of first assessment test (oPRE) and both PRE and FU (p=0.048 and p=0.025 respectively). The healthy limb did not change significantly over time.

The kinetic analysis of the gait showed deviation in term of ankle moment and power. Concerning the ankle moment (Fig. 3.12 a slight improvement (about 11%) for the healthy limb (p=0.01 between maximum values of PRE and FU) was observed, although it was maintained lower than the normality over time. The paretic ankle moment as well as the power were reduced with respect to the healthy subjects but no significant difference was found in terms of maximum values over time (Fig. 3.13).

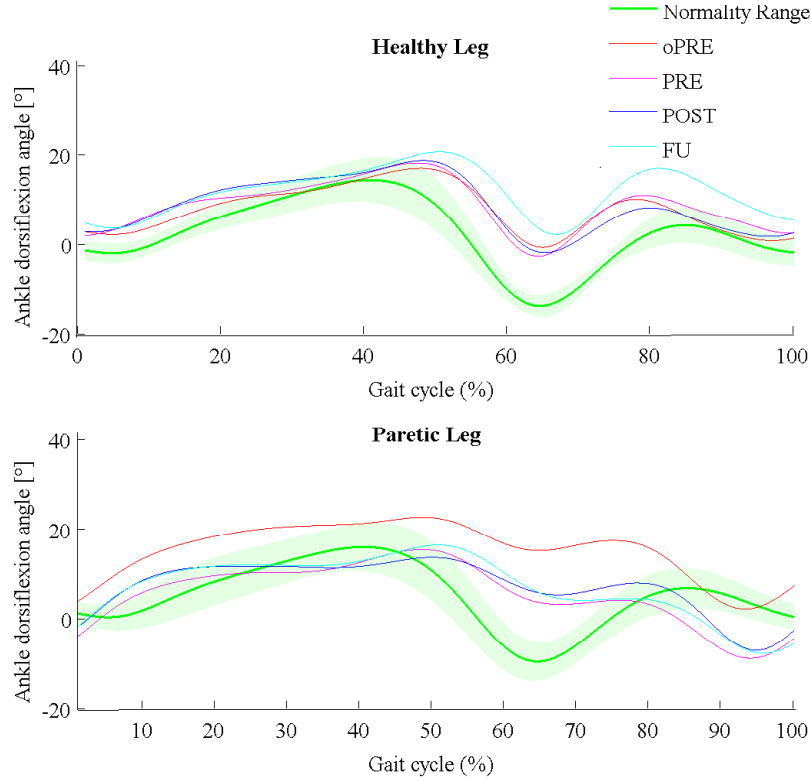


Figure 3.11: Angle of ankle dorsi (angle  $> 0$ ) and plantar (angle  $< 0$ ) flexion over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

Finally the analysis of the vertical forces (Fig. 3.14) for the healthy leg showed that both peaks were delayed before the training. After the treatment the push off peak was correctly anticipated. The paretic leg presented an anticipated push off peak during the oPRE and PRE that was correctly postponed after the treatment. Finally the maximum values of the two peaks for both the legs did not change over time.

Summarizing the gait analysis results, some evidence of improvement of ankle plantar-flexion angle were obtained between oPRE and PRE, thus not dependant from the treatment. Moreover kinetics and the vertical forces, although impaired at baseline, did not clearly showed an improving trend.

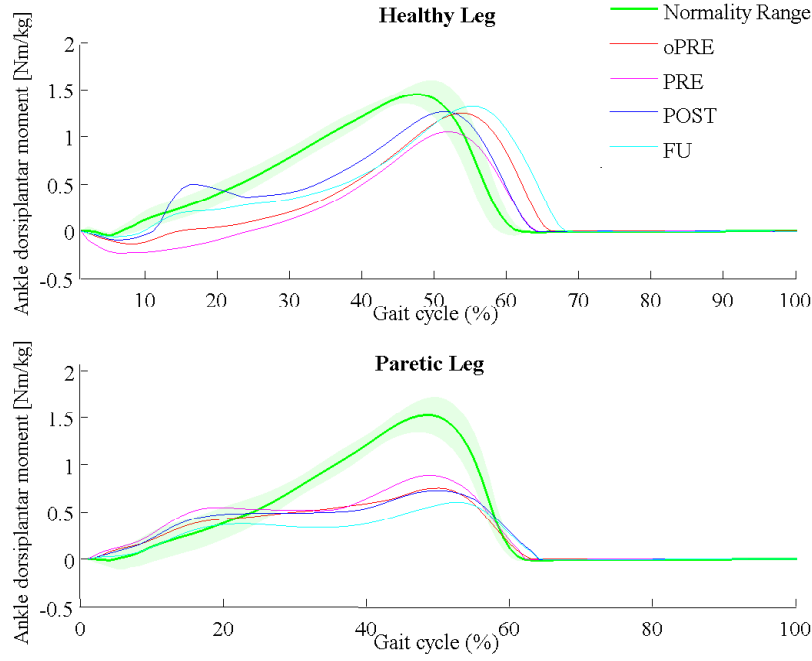


Figure 3.12: Ankle moment over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

### 3.3.2 Pedaling test

The results concerning the ability in maintaining the speed during volitional pedaling are shown in Tab. 3.10. Except in the first assessment test (oPRE), the speed was within the

	<b>oPRE</b>	<b>PRE</b>	<b>POST</b>	<b>FU</b>	<b>CG</b>
V [rpm]	33.92 (2.95)	30.12 (1.64)	29.98 (1.80)	30.96 (1.41)	30.64 (0.20)

Table 3.10: Comparison of velocity during pedaling within oPRE, PRE, POST and FU. The values are represented as median (inter-quartile ranges) obtained from the revolutions during each session.

control group ranges over time.

Fig. 3.15 shows the results in terms of mechanical work produced during pedaling..

In all the tests S2 produced an exaggerated amount of work with the healthy limb with respect to the normality ranges, mainly caused by an excessive production of pulling work that was maintained different from the CG ranges for all the assessments.



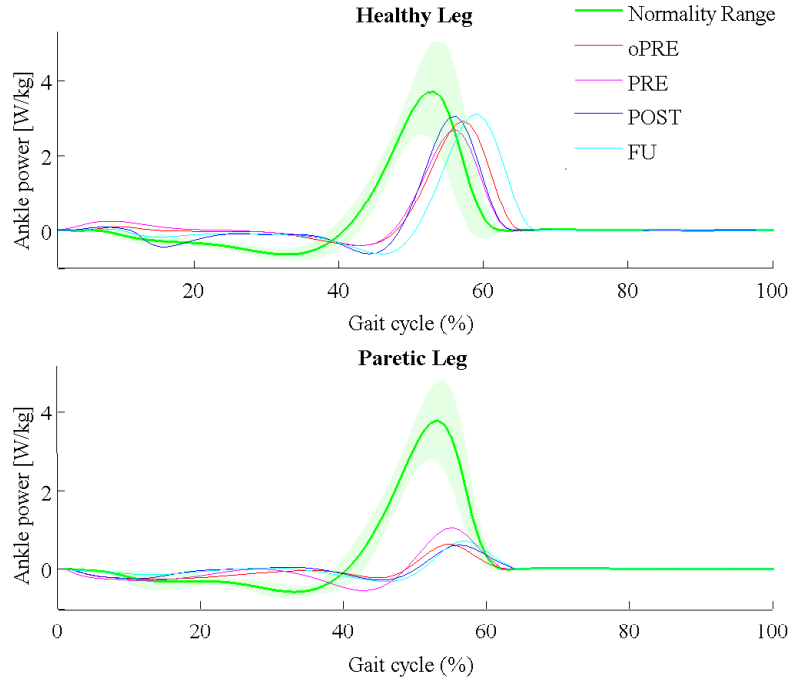


Figure 3.13: Ankle power over time. Median values are represented and compared with median and interquartile ranges of the control group.

Differently, the paretic limb maintained  $W_{TOT}$  within the normality ranges in all the assessment tests except oPRE. The unbalance was maintained significantly over normality ( $p < 0.01$ ) during all the tests although a significant reduction was shown between oPRE and the other tests caused by both a slight reduction of healthy leg and an increase of paretic leg. This effect is not imputable to the training as it occurred already at PRE test. The results of the EMG signal analysis is here presented using the normalization method based on the maximum peak of activation. Indeed the MVC values were not reliable as the rectus femoris, the vastus medialis and the biceps femoris showed an activation over the level obtained during the pedaling exercise.

The analysis of the EMG signal acquired on the healthy leg during pedaling is shown in Fig. 3.16. The profiles revealed that the onset of rectus femoris (RF) during oPRE and PRE tests were slightly phase advanced with respect to healthy subjects while the maximum of activation was correctly positioned. After the treatment a further advancement was shown (both POST and FU tests).

Similarly, the vastus medialis (VM) showed the activation during oPRE test almost cor-

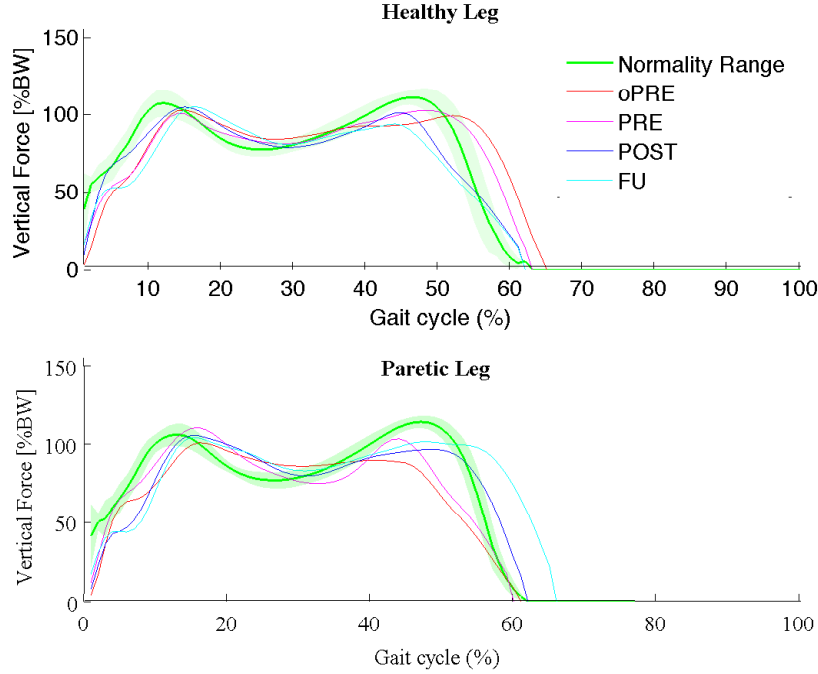


Figure 3.14: Vertical force over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

rectly synchronized with respect to CG. During POST and FU the profiles were slightly anticipated both in onset and offset of the activation.

Please note that the activation timing of RF was changed toward the VM profiles, probably caused by the synchronous activation of the quadriceps during FES.

The biceps femoris (BF) was characterized by oPRE test that showed a maximum activation correctly timed (but with a postponed offset) while the PRE had both onset and offset of activation postponed. The POST test revealed values within the CG ranges but the improvement was not maintained at FU. The tibialis anterior (TA) showed the maximum activation peak postponed both at oPRE and PRE. After the treatment a correct phase-advanced excitation was shown at POST test while a further anticipation occurred at FU. The gastrocnemius medialis (GM) was correctly activated at POST and FU while previous profiles were postponed.

The activation profiles of paretic leg are shown in Fig. 3.17. The RF at oPRE test was characterized by a prolonged activation out of the physiological ranges. This profile was not maintained at PRE test that only showed both onset and offset slightly postponed.

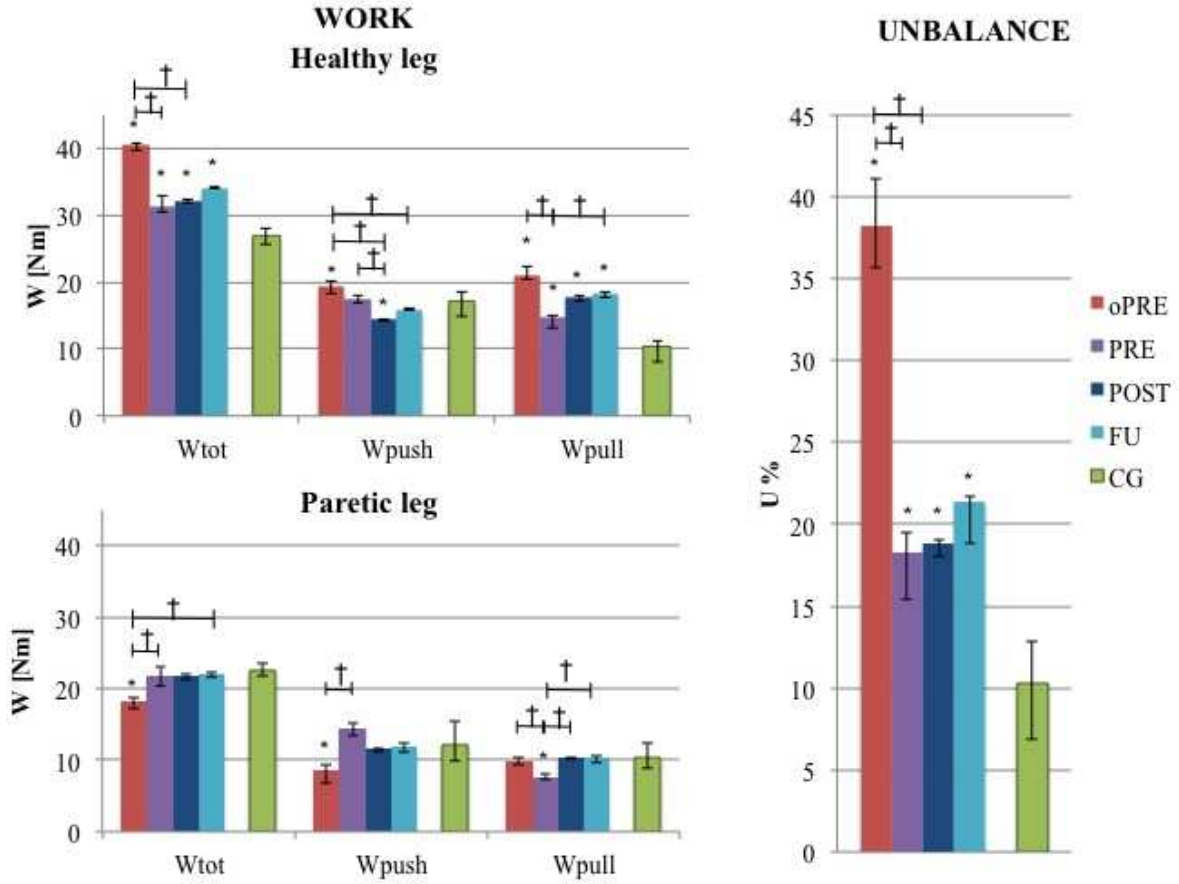


Figure 3.15: Work and unbalance  $U$  over time (coloured scale). The median and inter-quartile ranges (error bars) of the total work produced while the two legs as well as the pushing and pulling work are shown. The right panel represents the unbalance between the overall work of the two legs. † indicates significant difference ( $p < 0.05$ ) obtained with post-hoc analysis of Kruskal-Wallis test while \* indicates a significant difference with the control group (CG).

During the POST test a correct onset and an early offset occurred while the activation at FU was phase-advanced both for onset and offset although the maximum peak was correctly timed.

The VM profile was less impaired already at baseline and a correct activation was maintained at POST.

The activation peak of BF was phase-advanced at baseline and maintained similar values at POST and FU providing an action during the hip extension phases (I and II) while the knee flexion was not provided by this muscle, as it did not intervene in the pulling

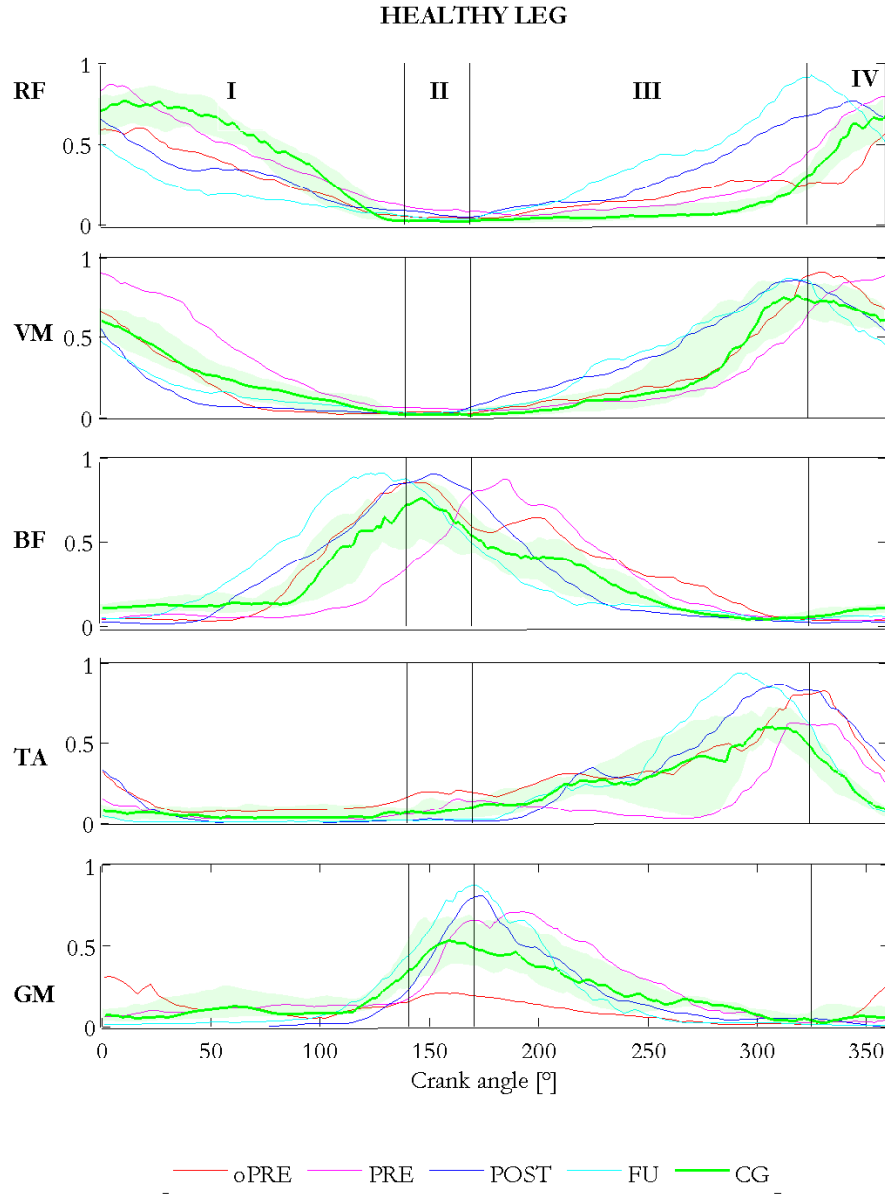


Figure 3.16: Median EMG profiles with respect to the crank angle of the five muscles for S2 healthy leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.

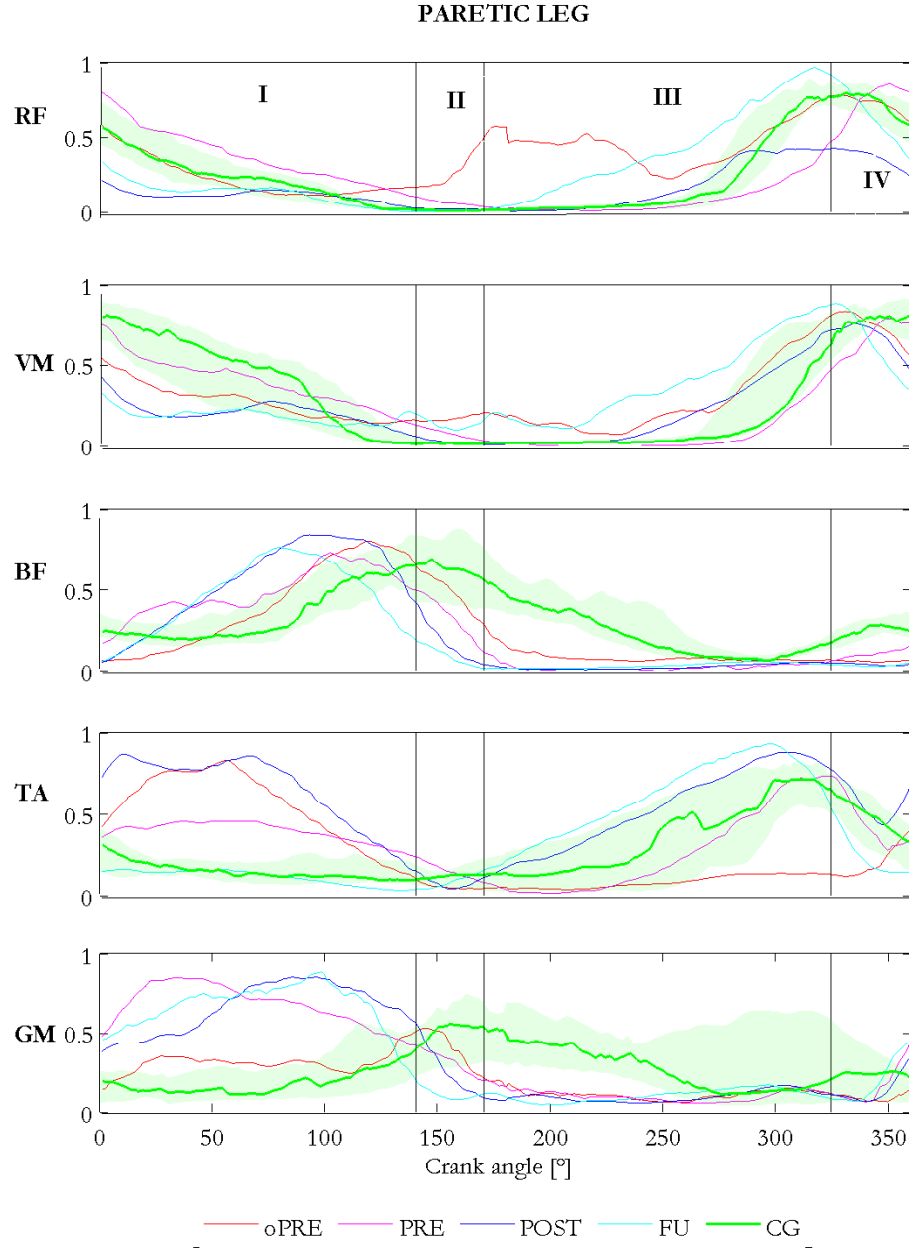


Figure 3.17: Median EMG profiles with respect to the crank angle of the five muscles for S2 paretic leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.

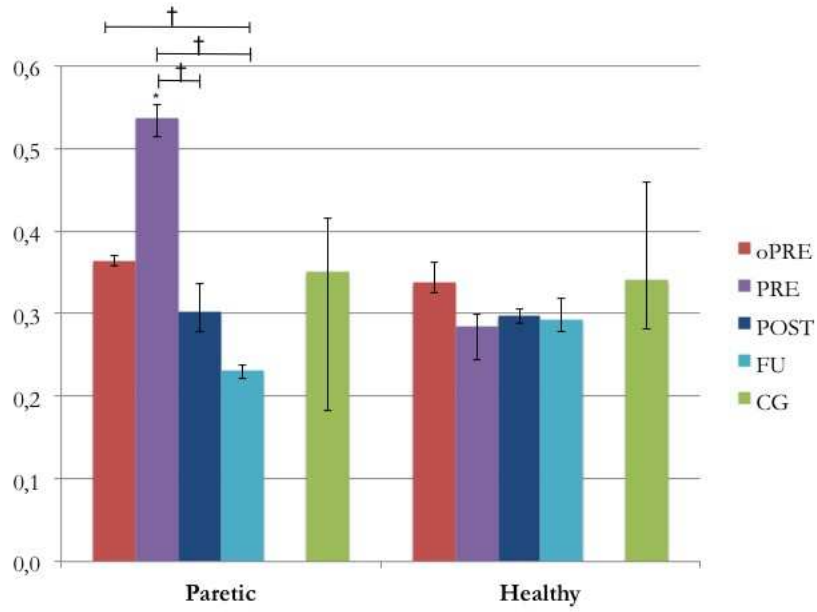


Figure 3.18: Co-contraction index of paretic and healthy legs of S2 is shown. † indicates statistical difference over time while \* between each test and the control group.

movement.

The TA was not correctly activated over time. In particular a prolonged excitation was provided during all the assessments but the FU. The GM showed an out-of-phase activation with respect to the control group maintained at all the assessment tests.

Summarizing, S2 showed some deviation at baseline and few changes occurred over time. In particular the proximal muscles analyzed was almost correctly timed after the treatment while the distal one maintained significant deviations.

Another observation is that, although no treatment occurred in the observation phase (between oPRE and PRE), S2 was characterized by different results between oPRE and PRE of both paretic and healthy legs.

Finally, from the profiles of RF and BF the co-contraction index was computed (Fig. 3.18). While the healthy limb was characterized by a co-contraction within the CG ranges over time, the PRE test of paretic leg showed a significantly higher values ( $p < 0.01$ ) with respect to all the other assessment tests. This peak was mainly caused by the early initiation of BF showed in the third panel of Fig. 3.17. The action of the couple of agonist-antagonist

was then restored and maintained over time.

### 3.4 Subject 3

The third patient was a 12 years old male and was affected by cerebral palsy with damage located in the right brain hemisphere with a consequent left side impairment. An overview of the clinical assessment over time is shown in Tab. 3.11.

Clinical Scale	oPRE	PRE	POST	FU	Ranges (Mild-Severe)
Winter Scale	I	I	I	I	I - IV
GMFM	99.21%	100%	100%	100%	100% - 0%
Boyd Test	3/4	3/4	3/4	3/4	4 - 0
OGS	12/19	12/19	12/19	12/19	22 - -2
Ashworth Scale	2/0	2/0	2/0	2/0	0 - 4

Table 3.11: Clinical assessment over time for Subject 3. The classification with the Winter scale and the results of GMFM, Boyd test, Ashworth scale and OGS are presented as paretic/healthy limb.

It can be noticed that subject 3 presented a slight disability already at baseline and no significant changes occurred over time. The spasticity level was higher than the one of subject 2, while the ability in performing the gross motor skill was maximum already in the PRE test. The most impaired score was gained in OGS test indicating a reduced performance in the walking ability that was maintained over time.

#### 3.4.1 Gait analysis

From the analysis of the spatio-temporal parameters (Tab. 3.12) a first quantitative information about the locomotion ability can be achieved.

The mean velocity  $V$  during gait had values just below the normality ranges and did not change significantly over time ( $p > 0.05$ ). The step length of both paretic and healthy limb was generally over normality ranges and did not change over time except for the step length of the healthy limb at FU that presented a significantly higher value. Consequently

	oPRE	PRE	POST	FU	CG	P-value	Post-Hoc
V [m/s]	1.18 (0.06)	1.17 (0.04)	1.11 (0.08)	1.16 (0.01)	1.31 (0.60)	0.622	
$L_{PL}$ [mm]	614.0 (20.0)	599.3 (16.5)	632.5 (16.1)	604.0 (28.1)	559.8 (48.0)	0.132	
$L_{HL}$ [mm]	643.0 (4.5)	685.0 (13.0)	628.3 (30.3)	725.0 (24.8)	559.4 (45.1)	<b>0.009</b>	POST vs FU p=0.009
SI [ ]	0.96 (0.04)	0.88 (0.02)	1.00 (0.04)	0.83 (0.04)	1.03 (0.23)	<b>0.011</b>	POST vs FU p=0.011

Table 3.12: Comparison of temporal-spatial parameters between oPRE, PRE, POST and FU. The values are represented as median (inter-quartile range) obtained during the different repetitions of each gait assessment. The Kruskal-Wallis statistical difference is shown as bold number and the post-hoc results are summarized.

the  $SI$  at FU was lower than the normality ranges and it was significantly different from the POST test that showed a perfect balance between the limbs.

Concerning the analysis of the kinematics during locomotion, distal impairment could be highlighted (Fig. 3.19).

In particular healthy leg showed a reduced range of motion (ROM) in the swing phase (except for PRE test) and the ROM of the paretic leg had more severe impairment. In fact the angle at initial contact was within the control group ranges for the healthy limb while the paretic limb showed an exaggerated plantar flexion, significantly improved over time ( $p=0.026$  for PRE vs FU, toward the CG ranges). Moreover, the profile during POST was maintained too high, while a significant improvement in term of range of motion ( $p=0.002$  in PRE vs FU post hoc) and maximum dorsiflexion in swing ( $p=0.021$  in POST vs FU post hoc analysis) was observed at FU, probably not related with the FES treatment.

The analysis of the kinetics showed some distal deviation, in particular concerning the production of the paretic limb ankle power at toe off (Fig. 3.20).

In fact, an insufficient propulsive power was produced over time although a improvement



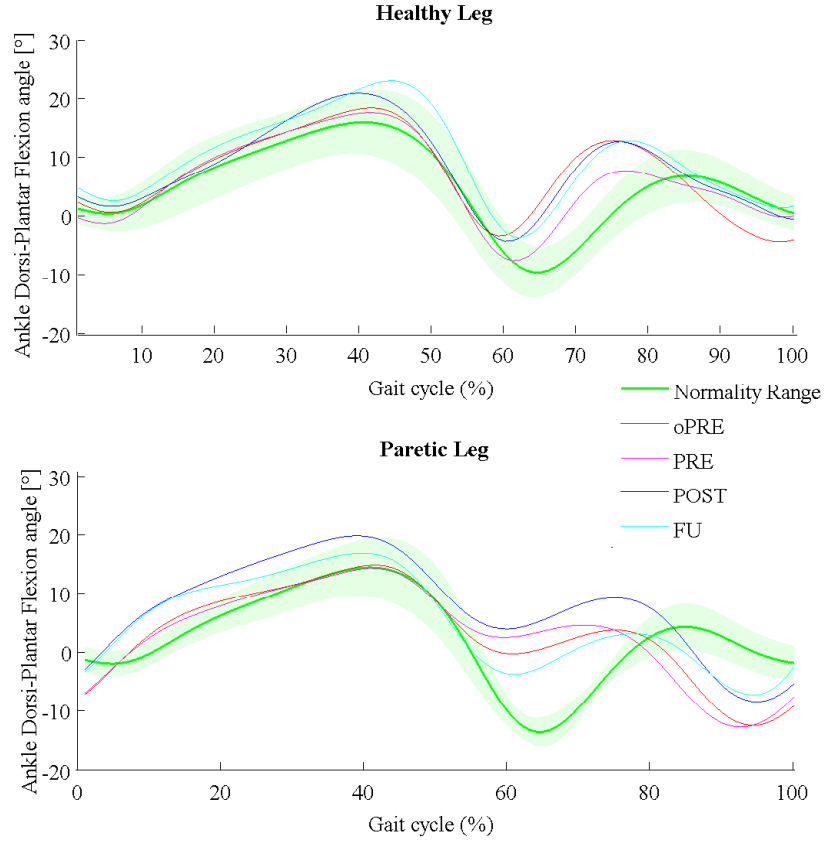


Figure 3.19: Angle of ankle dorsi (angle  $> 0$ ) and plantar (angle  $< 0$ ) flexion over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

of about 40% was highlighted between PRE and FU ( $p=0.022$ ).

Finally some deviations in the force exchanged with the ground was shown at baseline (Fig. 3.21). In particular the paretic limb profile presented a lower push-off peak with respect to the normality values while the healthy limb was maintained within the CG ranges over time (except during PRE test). Moreover the paretic limb during the PRE test showed a strategy quite different from the other sessions and significant differences were found in the peak values between PRE and POST ( $p=0.034$ ). In summary, the gait analysis presented some slight impairment at baseline and did not show relevant improvement over time.

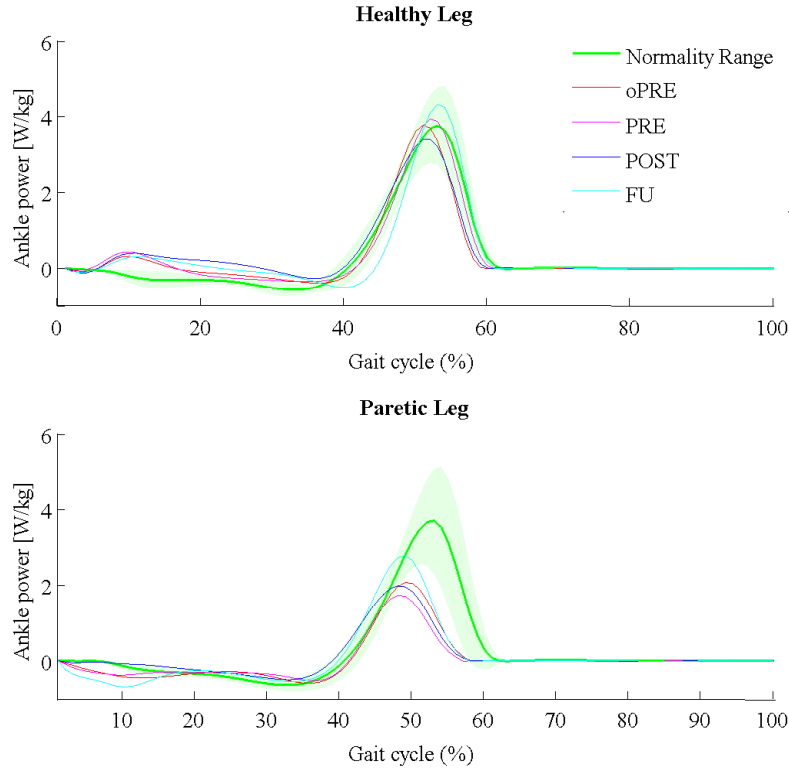


Figure 3.20: Ankle power over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

### 3.4.2 Pedaling test

During the pedaling assessments the ability in maintaining the speed was studied as shown in Tab. 3.13. The speed was maintained just below the control group ranges and the vari-

	oPRE	PRE	POST	FU	CG
V [rpm]	29.57 (1.38)	29.68 (1.49)	29.57 (1.33)	29.12 (1.29)	30.64 (0.20)

Table 3.13: Comparison of velocity during pedaling within oPRE, PRE, POST and FU. The values are represented as median (inter-quartile ranges) obtained from the revolutions during each session.

ability was higher than the one obtained by the healthy subjects.

The overall work (results summarized in Fig. 3.22) produced with the healthy leg was

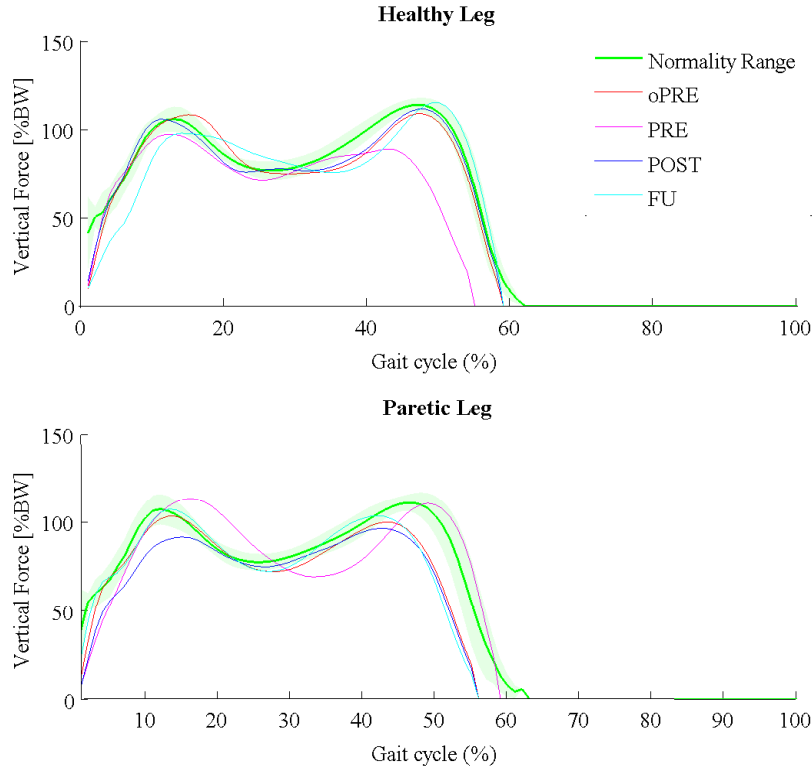


Figure 3.21: Vertical force over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

maintained just above the control group range (statistical difference assessed  $p < 0.01$  for all the assessment test).

During oPRE and PRE these values were due to an excessive production of work in the pushing phase. After training this component was decreased ( $p < 0.05$  for PRE and oPRE vs FU) towards the CG range but a concomitant significant increase (PRE and oPRE vs FU had  $p < 0.05$ ) in pull work occurred, maintaining an unvaried  $W_{TOT}$ . The paretic leg produced a total work below the normality ranges during all the tests. After the treatment a significant improvement (PRE vs POST had  $p < 0.05$ ) was found towards the healthy subject value although significant difference was maintained with the CG ( $p < 0.01$ ). This variation was due to an increased pull work in the POST test (oPRE vs POST had  $p < 0.05$ ) that was not maintained at FU. The unbalance assessed that a significant difference occurred between baseline versus POST and FU tests. The unbalance correctly

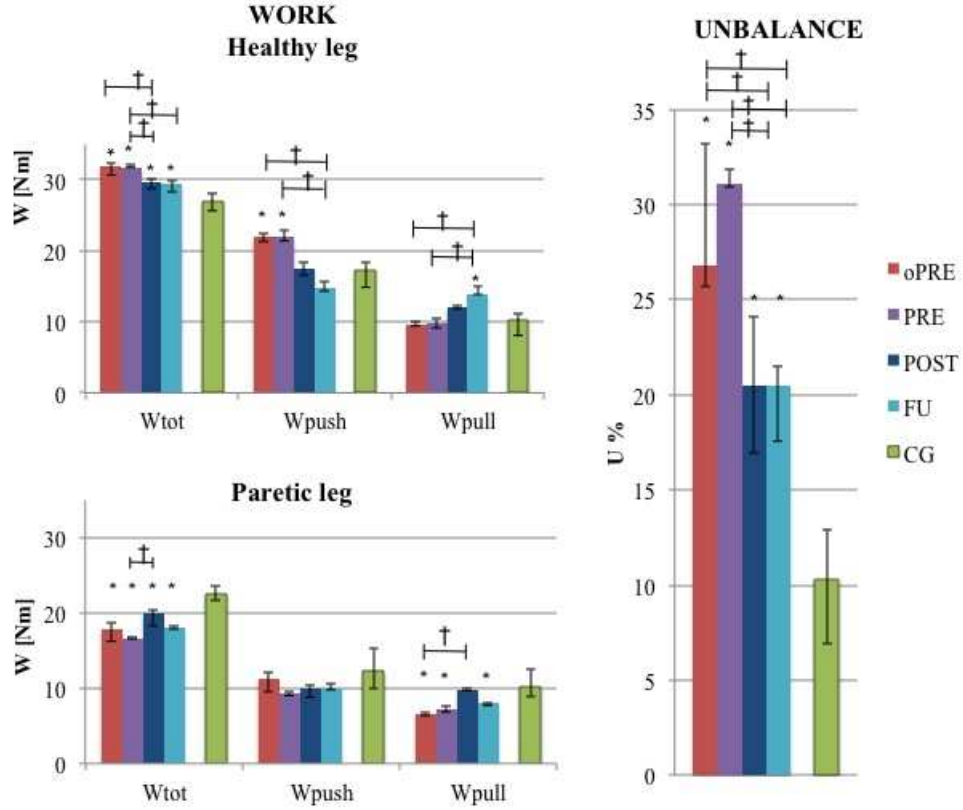


Figure 3.22: Work and unbalance  $U$  over time (coloured scale). The median and inter-quartile ranges (error bars) of the total work produced while the two legs as well as the pushing and pulling work are shown. The right panel represents the unbalance between the overall work of the two legs. † indicates significant difference ( $p < 0.05$ ) obtained with post-hoc analysis of Kruskal-Wallis test while \* indicates a significant difference with the control group (CG).

decreased after training and was maintained at FU.

The results concerning the EMG signals of both healthy and paretic legs are represented in Fig. 3.23 and 3.24, respectively. The subject was able to perform a reliable Maximum Voluntary Contraction test; thus a normalization with respect to MVC is here considered. Please note the different scale on the y axis that was preferred to provide a better graphical representation.

The healthy limb showed that the maximum peak of rectus femoris (RF) was phase-advanced at oPRE and PRE while a slight improvement was obtained over time with respect to the normality ranges. In terms of activation level some differences were ob-

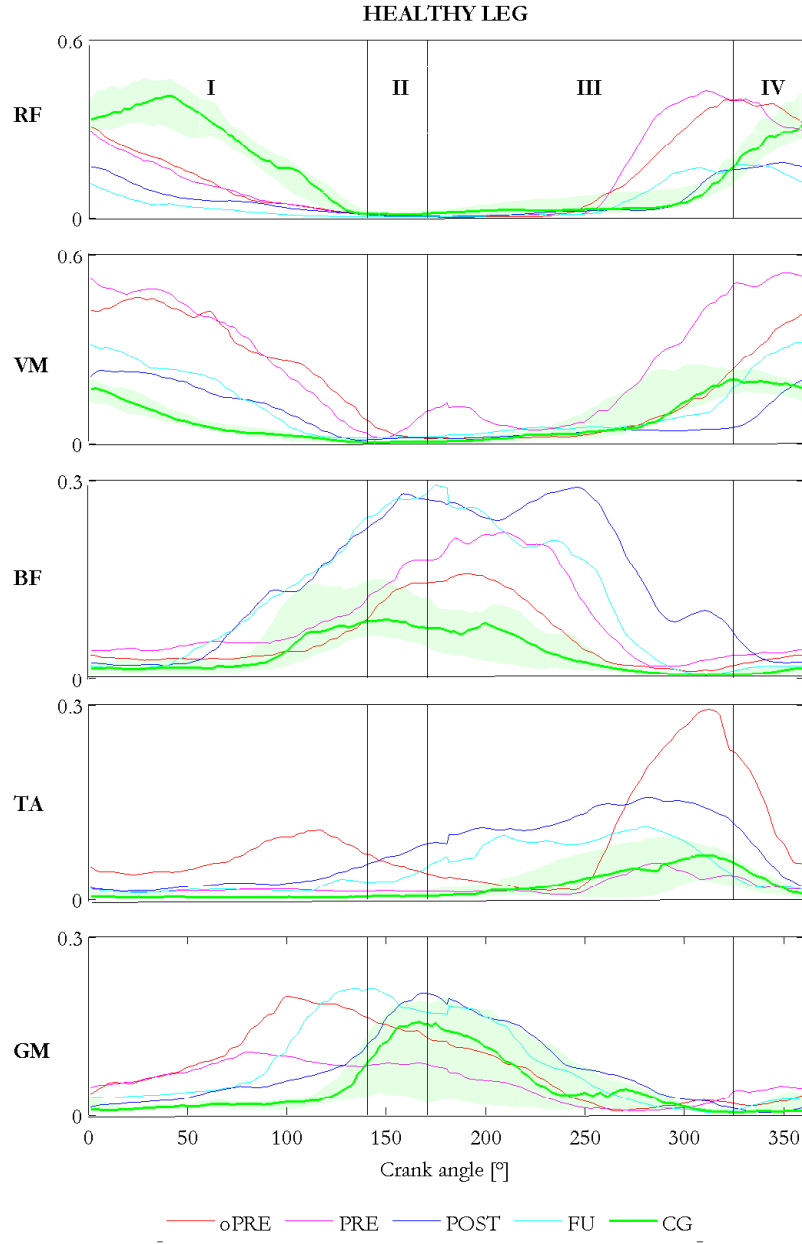


Figure 3.23: Median EMG profiles with respect to the crank angle of the five muscles for S3 healthy leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.

served: the maximum peak during oPRE and PRE tests were comparable to the CG while the POST and FU tests were activated at about 20% of their maximum level indicating a lower involvement of the healthy side.

A similar behaviour was obtained for the vastus medialis (VM). Moreover the activation timing of this muscles improved with respect to PRE test that showed a second prolonged activation peak between phases II and III.

Differently the activation level of BF was higher in POST and FU tests (about 30% of the MVC) with respect to oPRE, PRE and CG. Moreover during the POST test the offset was postponed obtaining a wider activation range.

Analysing the activation level of the proximal muscles, it can be observed a reduction of the quadriceps (RF and VM) activation level in correspondence to the decreased work in pushing phase and an increased activation level of BF while the work in pulling phase was augmented (see Fig. 3.22).

The tibialis anterior (TA) showed very different behaviour between oPRE and PRE profiles. The first one resulted in a prolonged activation while the second was within the CG ranges. A phase advanced excitation during POST and FU occurred and the activation level was slightly higher than the CG (the median values are 16%, 13% and 8% of the MVC respectively).

Finally the gastrocnemius medialis (GM) was characterized by a phase-advanced maximum peak both at oPRE and PRE tests. The POST test was correctly shifted within the CG ranges while the FU did not maintained the improvement. The median activation level was maintained just higher than the CG (about 20% for oPRE, POST and FU versus 15% of CG)

The activation profiles of paretic leg are shown in Fig. 3.24.

Similarly to the healthy limb, the RF showed a decreased muscular activation level during POST and FU tests, obtaining values comparable to the CG. Concerning the activation timing, the RF was maintained postponed with respect to the normality ranges. This mean that the RF intervened particularly providing the knee extension while during hip flexion was not active.

The activation timing of VM was more similar to the CG although a slightly phase-advanced. The level of activation was maintained within the CG over time.

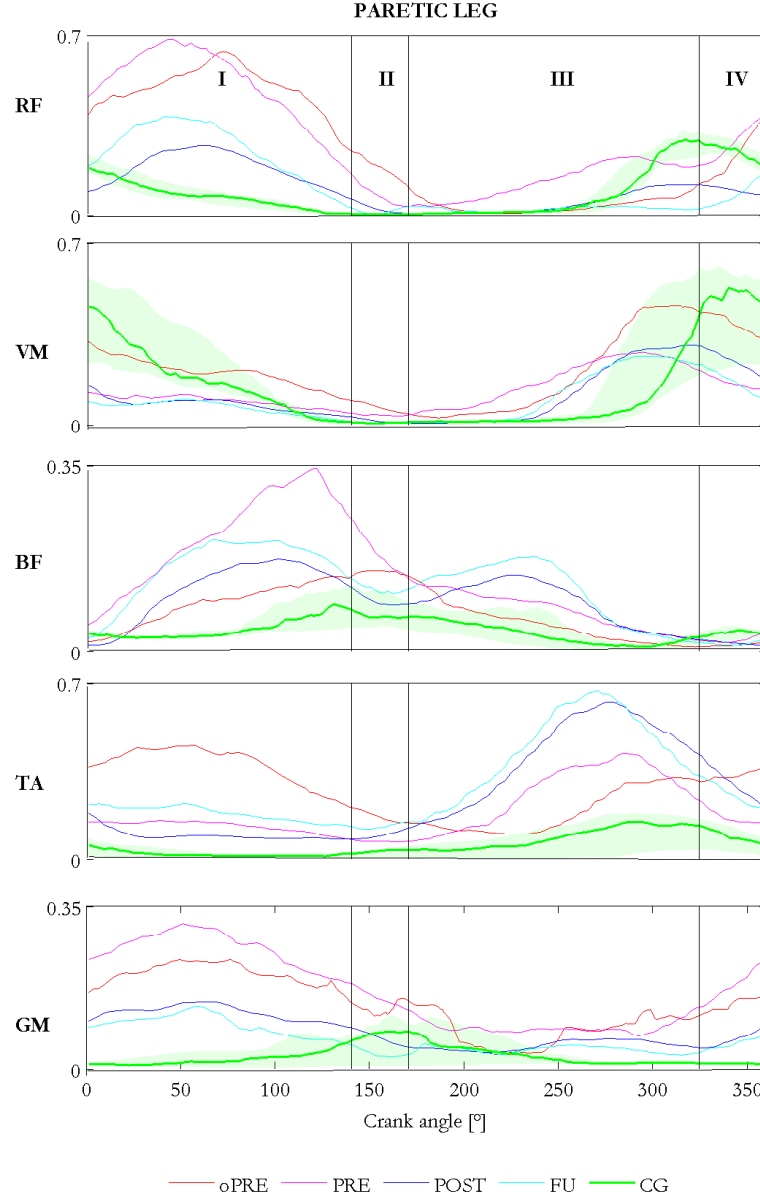


Figure 3.24: Median EMG profiles with respect to the crank angle of the five muscles for S3 paretic leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.

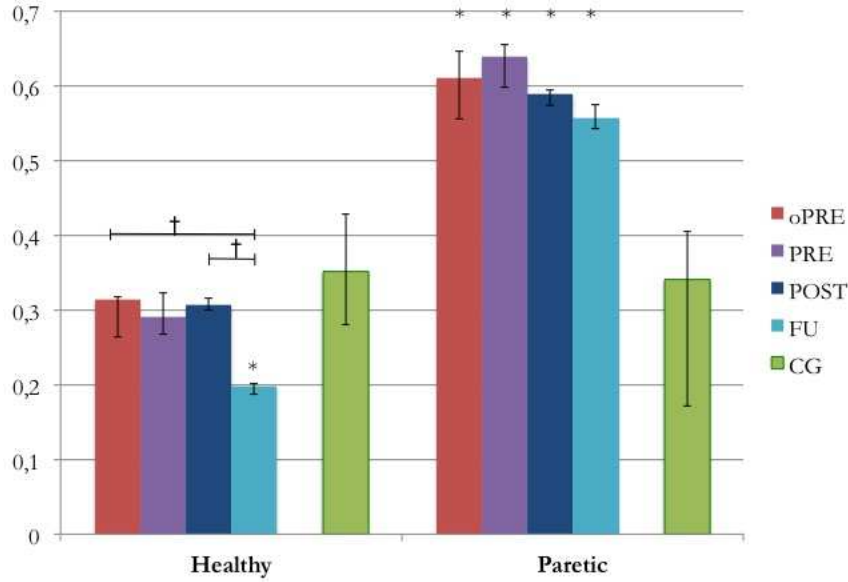


Figure 3.25: Co-contraction index of paretic and healthy legs of S3 over time is shown. † indicates statistical difference over time while \* between each test and the control group.

The BF showed a prolonged activation (I, II and III phases) but with low activation level as, except for PRE test, it reached maximum values included between 15% (oPRE) and 20% (FU) of the MVC.

The activation timing of TA was maintained during the tests but during the oPRE that showed a prolonged activation (III, IV and I phases). Finally the GM presented a shifted and prolonged activation that was maintained over time. The activation level during POST and FU was comparable to that of the CG.

Summarizing the results, it can be highlighted that the MVC normalization provide some information: at POST and FU test the EMG profiles of the RF and VM of both the legs were performed with a smaller relative activation level. Some impaired activation timing was highlighted but no changes occurred within the time.

The co-contraction between RF and BF is shown in Fig. 3.25. The healthy limb was within the normality ranges already at baseline and the value was maintained unvaried at POST test. The FU test was significantly different from the others and from the CG as the the rectus femoris at FU showed a reduced range of activation. Differently, the paretic leg showed an value higher than the one of the healthy subject that was slightly reduced



after the treatment (not statistically significant) due to an impaired activation strategy, as can be observed in Fig. 3.24.

### 3.5 Subject 4

The fourth subject that underwent the training was a 16 years old male that experienced an ischemic stroke at the age of 8. After the acute phase of the disease, he experienced a severe impairment at the upper limb while the lower limb maintained a better muscular tone and distal control. Details about the clinical situation of the subject over time are presented in Tab. 3.14.

Clinical Scale	oPRE	PRE	POST	FU	Ranges (Mild-Severe)
Winter Scale	II	II	II	II	I - IV
GMFM	100%	99.72%	99.50%	99.50%	100% - 0%
Boyd Test	3/4	3/4	3/4	3/4	4 - 0
OGS	17/21	17/21	17/21	17/21	22 - -2
Ashworth Scale	3/0	3/0	3/0	3/0	0 - 4

Table 3.14: Clinical assessment over time for Subject 4. The classification with the Winter scale and the results of GMFM, Boyd test, Ashworth scale and OGS are presented as paretic/healthy limb.

As the Winter scale showed, the locomotion ability of the subject was affected by drop foot and impaired ankle plantar flexion in stance phase. S4 was able to perform almost all the gross motor skills assessed with GMFM already at baseline and a good distal control was achieved as the patients could perform the ankle dorsiflexion with only a slight contribution of knee flexion (Boyd test).

The spasticity of the paretic limb was relevant and the score obtained with the Ashworth classification was 3. As the subject's condition was borderline with respect to the inclusion criteria, he was included in the study but a customized treatment was performed. In fact, particular care was employed in electrodes positioning in order to avoid the occurrence of spasm during training. Nevertheless 3 out of 21 FES-cycling sessions were performed with-

out the volitional contribution to the pedaling as an increased muscular stiffness occurred when voluntary contribution was added to FES, preventing the patient to continue.

### 3.5.1 Gait analysis

The locomotion ability was quantitatively assessed over time. The results concerning the gait spatial temporal parameters are reported in Tab. 3.15.

	<b>oPRE</b>	<b>PRE</b>	<b>POST</b>	<b>FU</b>	<b>CG</b>	<b>P-value</b>	Post-Hoc
V [ <i>m/s</i> ]	1.18 (0.04)	1.24 (0.05)	1.23 (0.03)	1.28 (0.03)	1.31 (0.60)	0.622	
$L_{PL}$ [ <i>mm</i> ]	659.0 (12.0)	681.3 (21.5)	646.5 (27.1)	632.0 (16.1)	559.8 (48.0)	<b>0.010</b>	PRE-POST $p=0.035$ ; PRE-FU $p=0.020$
$L_{HL}$ [ <i>mm</i> ]	628.0 (7.5)	591.0 (19.0)	620.3 (20.3)	649.0 (5.5)	559.4 (45.1)	<b>0.005</b>	PRE vs FU $p=0.035$
$SI$ []	1.05 (0.01)	1.15 (0.03)	1.03 (0.02)	0.97 (0.02)	1.03 (0.23)	<b>0.006</b>	PRE vs FU $p=0.005$

Table 3.15: Comparison of temporal-spatial parameters between oPRE, PRE, POST and FU. The values are represented as median (inter-quartile range) obtained during the different repetitions of each gait assessment. The Kruskal-Wallis statistical difference is shown as bold number and the post-hoc results are summarized.

The mean velocity showed a positive trend toward the CG ranges although no significant difference ( $p>0.05$ ) could be observed over time. The step length of both paretic and healthy leg were either included the interquartile ranges or just above. The  $SI$  was included within the ranges of control group although the PRE test value was significantly different with respect to the FU. Comparing this information with the mean velocity, it can be asserted that, during the FU test, the patient step length was longer but with minor cadence.

The kinematic analysis assessed that changes occurred concerning the ankle dorsi-plantar flexion angle (Fig. 3.26).

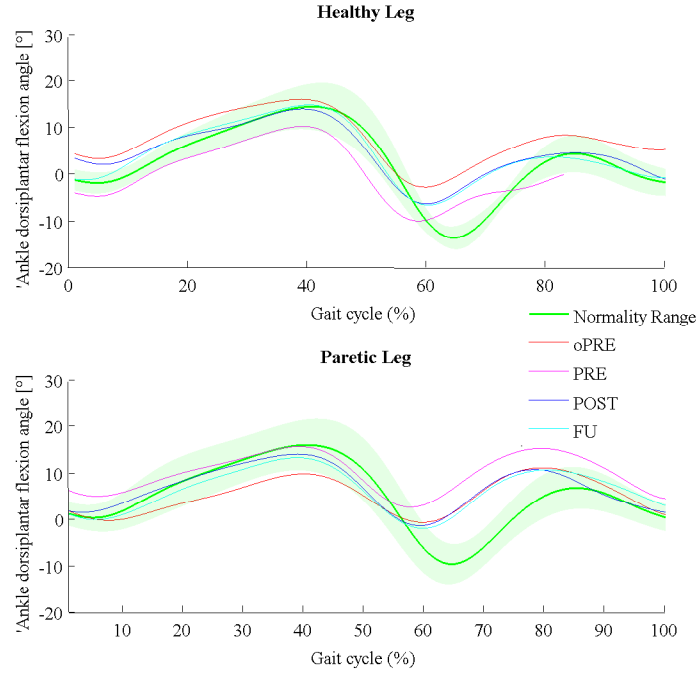


Figure 3.26: Angle of ankle dorsi (angle  $> 0$ ) and plantar (angle  $< 0$ ) flexion over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

In particular the healthy leg had impaired angles during swing phase while after the treatment a significant change in the normality direction was shown (PRE vs POST  $p=0.006$ ). Anyway, the more stressed variation did not depend from the training as occurred between oPRE and PRE (initial contact showed  $p=0.002$ , the maximum dorsiflexion in stance was different with  $p=0.004$  while in swing both maximum dorsiflexion and minimum plantarflexion had  $p=0.027$  and  $0.002$ , respectively). The paretic leg presented during PRE test an impaired initial dorsiflexion angle that was significantly different in the other tests (oPRE vs PRE with  $p=0.034$  and PRE vs POST with  $p=0.002$ ). Moreover the maximum flexion angle in stance and in swing were impaired during PRE and oPRE respectively. During swing a significant improvement after the treatment was shown (PRE vs POST  $p=0.018$ ). Concerning the range of motion some improvement have been observed in stance (oPRE-POST had  $p=0.005$ ) while a reduced ROM was maintained during swing. The ankle power produced during push-off was also analyzed (Fig. 3.27).

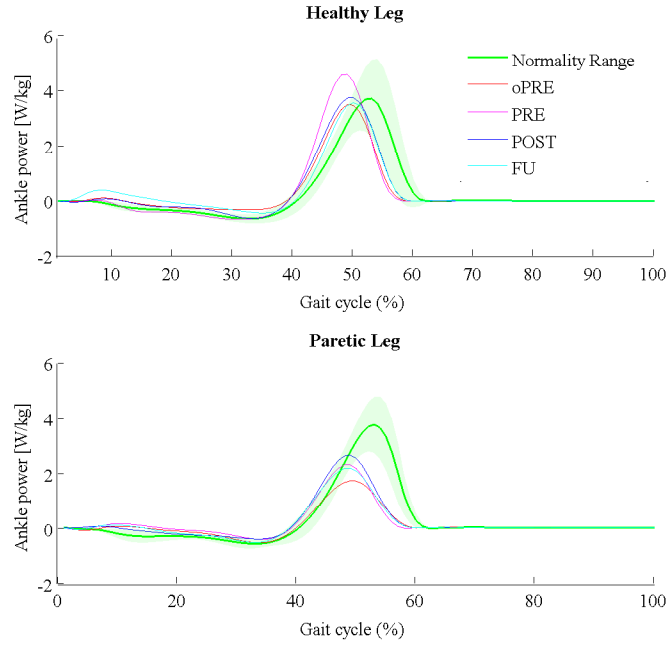


Figure 3.27: Ankle power over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

For both healthy and paretic leg, a phase-advanced of the peak was shown. The healthy side presented a maximum within the control group ranges while the paretic value was lower. A significant improvement of the paretic side was highlighted between oPRE and POST ( $p=0.005$ ) obtaining a relative increase between the two peaks of 33%.

Finally the vertical forces exchanged to the ground in stance phase was observed (Fig. 3.28). The healthy leg was able to produce a higher amount of force after the treatment in loading response (increase of 25%) while during the push-off phase no significant difference was found. The paretic leg had a peak value in loading response within the CG range already at baseline while the push-off peak was improved of 11% after the treatment (PRE-FU  $p=0.003$ ).

Therefore, the gait analysis highlight only slight improvement, often occurred already between oPRE and PRE thus not attributable to the treatment.

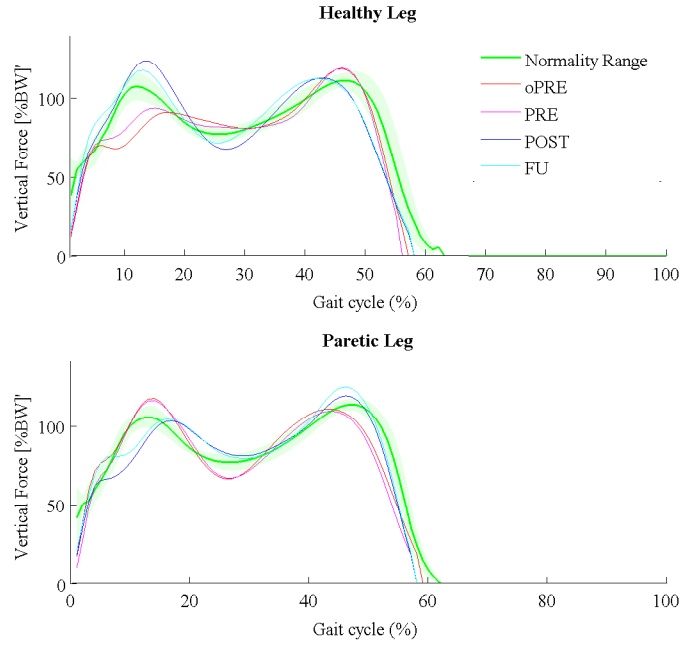


Figure 3.28: Vertical force over time. The chosen repetition of each gait assessment is represented and compared with mean and standard deviation of the healthy subjects.

### 3.5.2 Pedaling test

The first outcome of the pedaling test concerned the ability in maintaining the speed (Tab. 3.16).

	<b>oPRE</b>	<b>PRE</b>	<b>POST</b>	<b>FU</b>	<b>CG</b>
V [rpm]	28.96 (2.26)	29.55 (2.62)	29.22 (1.58)	28.51 (1.66)	30.64 (0.20)

Table 3.16: Comparison of velocity during pedaling within oPRE, PRE, POST and FU. The values are represented as median (inter-quartile ranges) obtained from the revolutions during each session.

The median velocity maintained by S4 during the four assessment tests did not changed over time and had a higher variability with respect to the control group speed.

More interesting results were observed from the analysis of the work produced by healthy and paretic legs (Fig. 3.29).

The work of the healthy limb was maintained above the normality ranges for all the tests

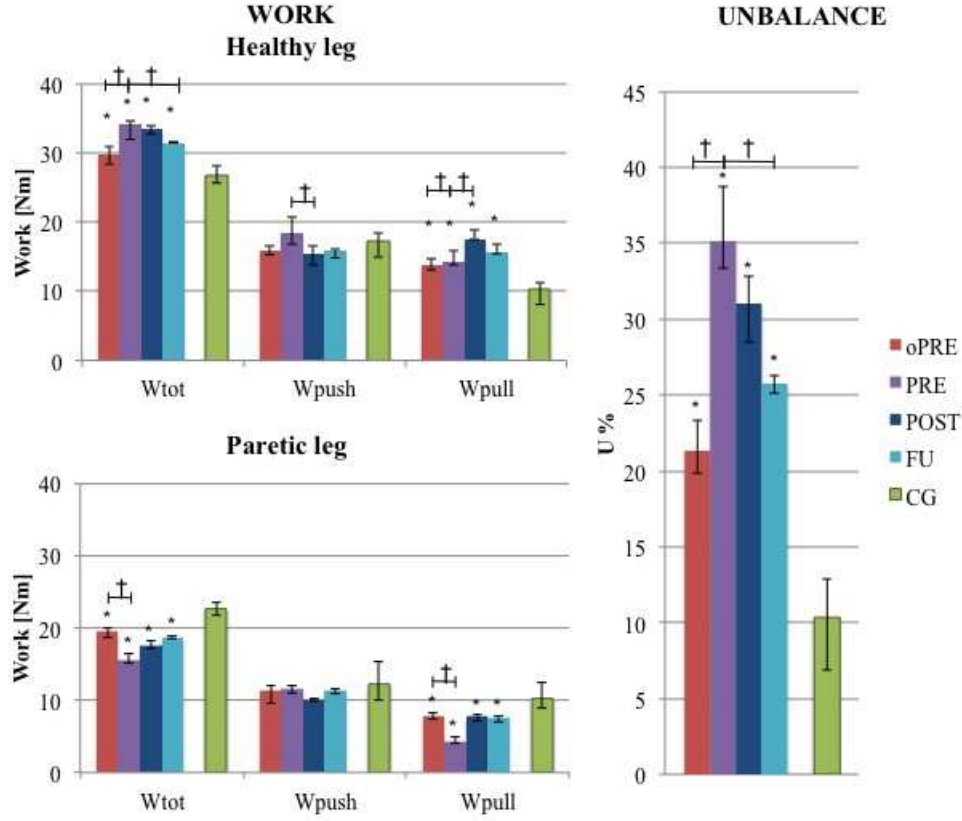


Figure 3.29: Work and unbalance  $U$  over time (coloured scale). The median and inter-quartile ranges (error bars) of the total work produced while the two legs as well as the pushing and pulling work are shown. The right panel represents the unbalance between the overall work of the two legs. † indicates significant difference ( $p < 0.05$ ) obtained with post-hoc analysis of Kruskal-Wallis test while \* indicates a significant difference with the control group (CG).

concerning both  $W_{TOT}$  and  $W_{PULL}$  while  $W_{PUSH}$  was included within the CG ranges over time. Therefore the healthy limb of S4 correctly pushed the pedal but produced an exaggerated amount of work during the pulling phase causing an overall amount of work higher than normality ranges. Concerning the paretic leg,  $W_{PUSH}$  was correctly performed while the values of  $W_{TOT}$  and  $W_{PULL}$  were maintained just below the normality ranges and were always significantly different from the control group ranges.

The unbalance was significantly increased between oPRE and PRE while after the treatment it was progressively decreased. All the values were maintained significantly above the control group ranges.

The analysis of the EMG signal is presented in Fig. 3.30 and 3.31. During all the four assessment tests, the MVC values obtained by S4 on the five muscles analysed were above the activation level achieved during cycling. Thus the EMG signals were normalized with respect to the MVC.

The healthy leg rectus femoris (RF) showed a postponed onset and offset at oPRE and PRE. After the treatment the profiles of the POST test was exactly within the CG ranges and the improvement was maintained at FU. The activation levels of oPRE, PRE and FU were comparable and slightly below the normality ranges.

The vastus medialis (VM) during oPRE and PRE obtained two well timed profiles but with very different level of activation (maximum peak was at 40% and 7% of the MVC respectively). After the treatment the profiles showed activation level comparable to the CG but slightly early terminated.

From the behaviour of biceps femoris (BF) some differences were observed over time. In particular the oPRE and PRE tests were both well timed even if with different activation levels. After the treatment a phase advanced of the onset of activation occurred, obtaining values different from the CG ranges.

The tibialis anterior (TA) was well timed at oPRE and partially at PRE test. During the POST test prolonged excitation was shown while the FU obtained a profile only slightly phase advanced.

Finally the activation of the gastrocnemius medialis (GM) was maintained over time during phase I, resulting to be anticipated with respect to the CG both in terms of onset and offset.

The activation profiles of the paretic leg are shown in Fig. 3.31.

At baseline the RF was characterized by a correct timing while after the treatment the profiles were phase-advanced both at onset and offset. The level of activation was maintained just below the CG ranges for all the assessment tests.

Similarly to the healthy leg, the VM of the paretic leg showed a very different level of activation between oPRE and PRE while the timing of activation was correctly maintained over time.

The BF showed an activation level similar to the CG that was maintained for all the assessment. Also the activation timing was correct (except for the PRE test).

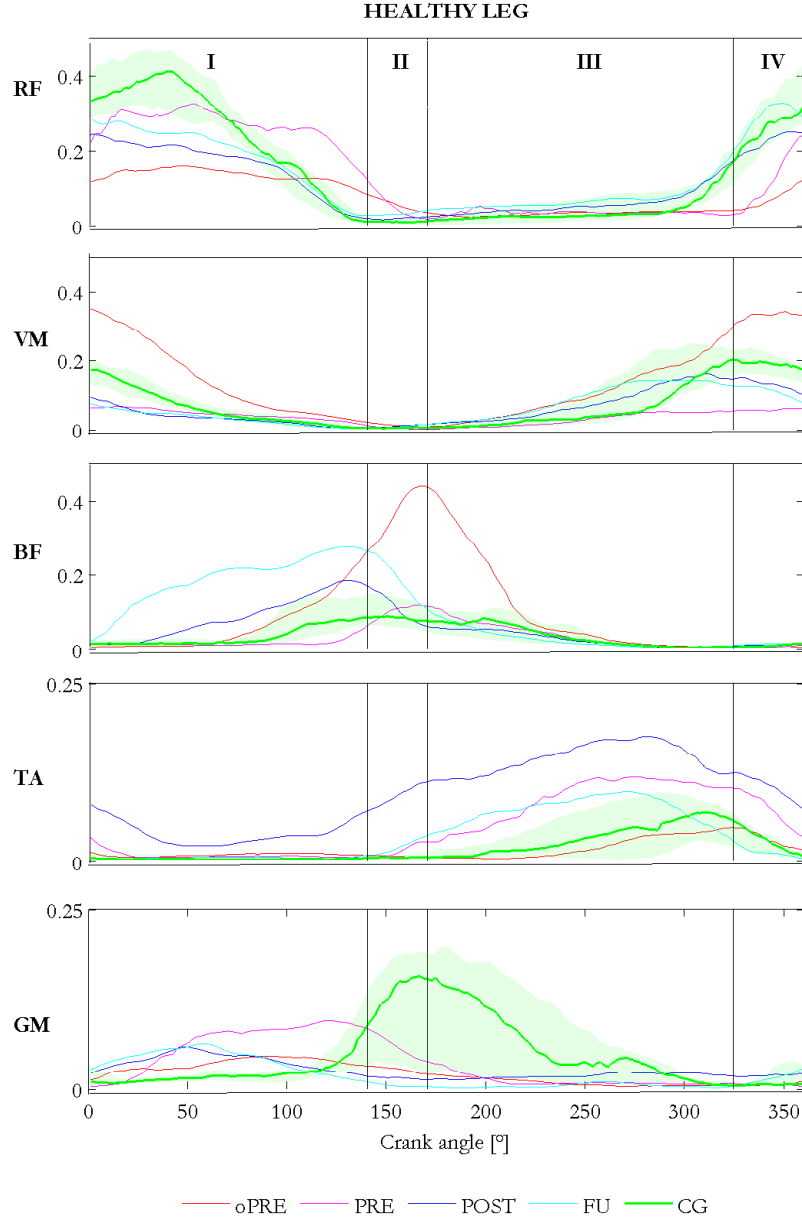


Figure 3.30: Median EMG profiles with respect to the crank angle of the five muscles for  $S_4$  healthy leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.



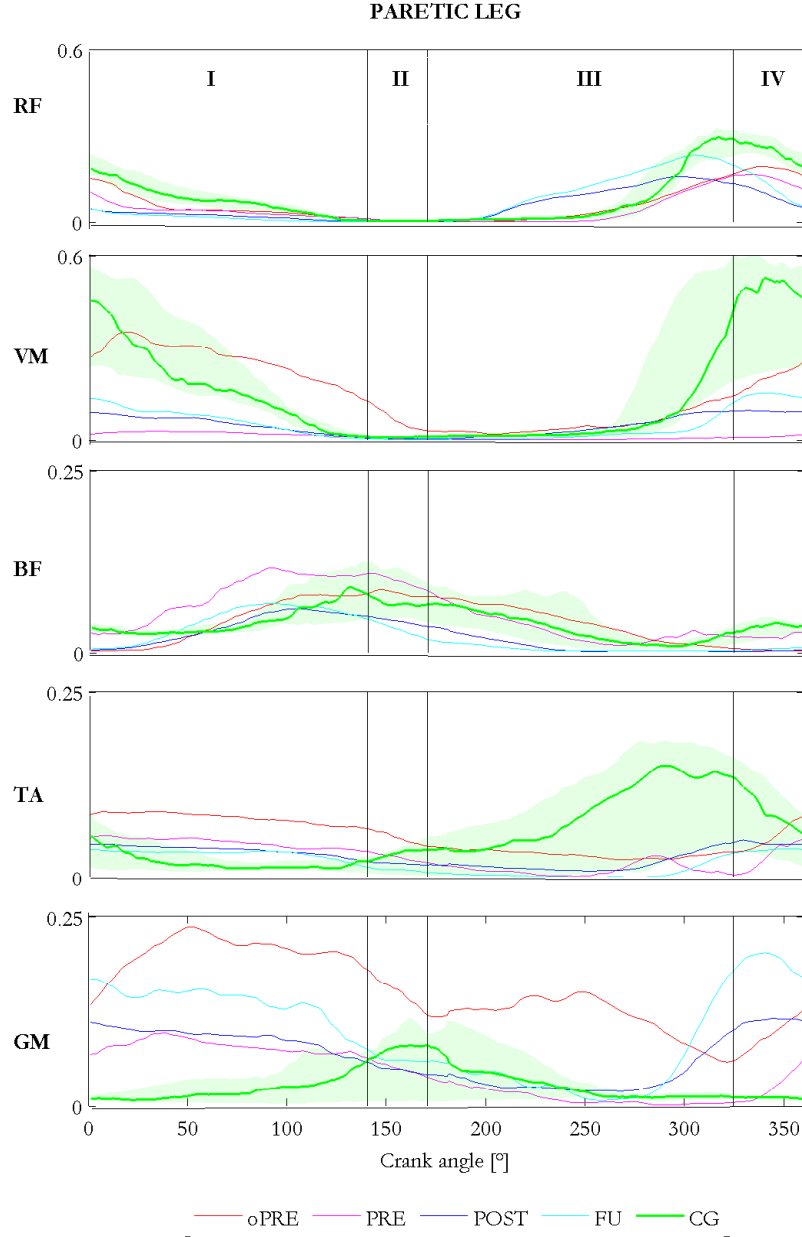


Figure 3.31: Median EMG profiles with respect to the crank angle of the five muscles for  $S_4$  paretic leg.  $0^\circ$  represent the crank angle that corresponds to the maximum flexion of the hip. Normalization of the EMG profiles was performed with respect to the maximum activation value (paragraph 2.3.3). Median and interquartile ranges of the control group are represented as bold green line and green area respectively.

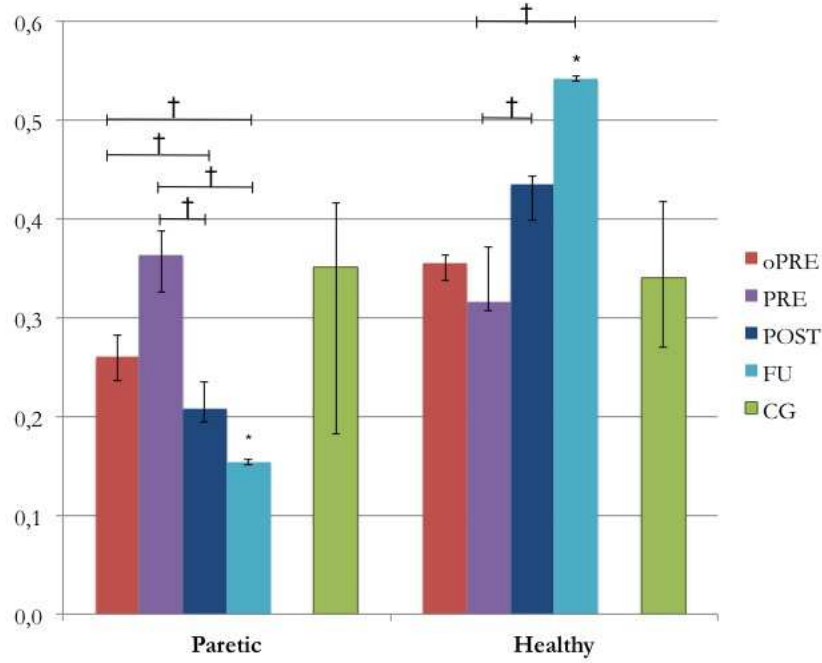


Figure 3.32: Co-contraction index (CCI) of paretic and healthy legs of S4 is shown. † indicates statistical difference over time while \* between each test and the control group.

Both TA and GM were out-of-phase and did not improve over time. The activation levels of TA was maintained nearby the first quartile of CG (maximum peak at about 5% of MVC but for PRE test that was at about 9%). Anyway the reliability of these results were uncertain due to the high variability of the TA and GM profiles (interquartile ranges are not shown in figure for clarity of representation) together with the low activation level. Summarizing the results, S4 presented some impairment in both healthy and paretic leg. Slight improvement was obtained in some of the proximal muscles of the healthy leg while the distal muscles did not show a trend toward the CG profiles. Moreover the high variability and the low level of activation of TA and GM confused the interpretation of their results.

The co-contraction index summarized the relationship between the profiles of RF and BF (Fig. 3.32). The CCI was maintained in the CG ranges over time but for the FU that moreover showed different behaviour for paretic and healthy legs. Analysing the profiles in Fig. 3.30 and 3.31 the healthy leg presented a phase advanced activation of BF that provided the hip extension in I phase. The paretic leg had deviation in the RF profiles

that was activated during hip flexion (III phase) more than the control group. Thus the agonist-antagonist strategy was not correctly timed during this test.

## Chapter 4

# Conclusion and future developments

The current work is focused on the assessment of the potential benefit induced by an intervention of FES-augmented volitional cycling in the rehabilitation of young hemiparetic subjects.

The effectiveness of FES in the hemiparetic rehabilitation is supported by a number of studies. One of the most interesting aspect of the FES training is the “carry over” effect that is achieved stimulating the neuroplasticity. This effect is further improved if FES is synchronized with volitional movement. Thanks to the greater flexibility of their central nervous system, the young subjects could obtain further benefit from an FES training. However, up to now only few studies evaluated the effectiveness of FES treatment in young hemiparetic subjects.

In order to improve the locomotion ability, FES-augmented voluntary cycling was chosen as it provides a kinematic pattern very similar to the walking involving a number of muscular groups activated in a coordinated and repetitive manner. Moreover it is a safe and widely accessible alternative to the FES-induced gait training.

Since only few studies in literature explored the application of FES treatment on young subjects, the target patients chosen for the present work was composed by six hemiparetic adolescents who underwent to a seven week FES-augmented volitional cycling treatment. The stimulation was delivered three times a week and each session lasted 30 minutes in-

cluding 5 minutes to worm-up the muscles (passive pedaling), 20 minutes of FES with voluntary pedaling and 5 minutes of worming-down (passive pedaling again).

The feasibility of the intervention was analysed. All the six patients well tolerated the stimulation and no limitation was highlighted but for one patient that was characterized by a moderate spasticity (Ashworth scale equal to 3). Anyway, the training on this subject could be carried out with particular care in electrodes positioning and, if necessary, with no voluntary contribution to the pedaling. Two out of six patients withdrew with the study after two week of FES intervention. The two patients showed only few impairment at baseline and their everyday life was not significantly limited by the disease. Thus, although the FES session did not cause any pain sensation and the muscles correctly responded to the stimulation, the two subjects stopped the training as the effort required to the patients and their family for reaching the rehabilitation center was not well-accepted. In conclusion, the feasibility of an FES-augmented volitional cycling treatment was assessed because the training was well tolerated. As the training was safe and the instrumentation was quite low-priced, such a training might be performed at home, thus minimizing the loss of time both for young patients and for their family.

The study design planned 4 assessment sessions, two before the training and two after the training. During the first two assessment tests, observational PRE (oPRE) and PRE, information on the changes in the subjects' performance not dependent to the training was achieved. The POST and FU sessions provided information about both short term and long term changes, induced by the training.

Different aspect of the motor problems was assessed during this tests. During the study both healthy and paretic limb were analyzed. In fact, as the subjects presented a chronic impairment, some compensation strategies could occur.

Clinical tests were performed in order to supervise changes in muscular spasticity, gross motor skills and locomotion ability. The results showed that all the patients presented a slight disability at baseline obtaining score just below the maximum achievable. None of the patients showed differences in the clinical indexes over the time.

Gait analysis was performed to quantitatively evaluate walking ability, which is the main goal of the lower limb impaired subjects. In particular, the results obtained showed that all the subjects were able to walk at a speed (about 1 m/s) just below the normality

ranges already at baseline and no changes occurred over time. According to a previous study [11] the speed value obtained was characteristic of people with lack of substantial limitations. The step length of the paretic and healthy leg showed slight deviation already during oPRE and PRE tests. A symmetry index (SI) was computed as ratio between the step length of the paretic and healthy leg. For all the subjects the values of symmetry was maintained within the CG ranges but in two out of four subjects a different strategy occurred over time. In fact in these cases the step length of paretic leg was maintained inferior than the healthy leg during oPRE, PRE and POST test while at FU become longer than the healthy step length. However, this change can not be ascribed to the training. The analysis of the kinematics during gait showed deviation in the angle of dorsi-plantarflexion for all the patients both for the healthy and paretic leg. Some statistically significant improvements due to the treatment in terms of minimum dorsiflexion angle were obtained for one out of four patients.

The kinetics data showed a reduced ankle power during the push-off phase, particularly for the paretic limb. Two out of four patients significantly improved the ankle power produced during POST test but the results were not maintained at FU. The relative increasing values at POST were of 25%, and 33%.

Finally, the vertical forces showed different behaviours for the subjects. Only one of the patients showed for both the legs some increase in POST and FU tests, that could be ascribed to the training.

An interesting observation was obtained comparing the results between oPRE and PRE tests. In fact significant difference often occurred between this two tests in all the subjects making difficult the interpretation of the results. During a previous study [71], the repeatability intra-subject of the gait analysis on 20 young subject affected by cerebral palsy was found significantly higher than that obtained on a group of 20 age-matched healthy subjects. In particular the kinematic data were less repeatable than kinetic. This could affect the reliability of some of the data obtained. Indeed only slight variation was observed thus they could be attributed to the variability of the measures.

The last assessment test was performed in order to evaluate the performance during cycling as it is the exercise directly trained during the treatment. Six age-matched healthy subjects was tested as a control group in order to obtain the normality ranges.

The amount of work produced during cycling by the healthy leg was maintained above the control group ranges for three out of four patients. In particular that was caused by an increased pulling work during pedaling that partially substitutes the paretic leg work that was below the normality ranges for three out of four patients. After the treatment some improvement was highlighted for two subjects although none of them was completely recovered.

An index of the symmetry of the cycling performance was also assessed. In particular, the unbalance between the work on the two legs was evaluated. Only one of the subjects presented values within the normality ranges at baseline while the values of all the others were significantly higher. Some improvement after the training was obtained for only one of the subjects, although the values were maintained significantly different from the normality.

The analysis of the muscular activations was performed recording the EMG signals of 5 lower limb muscles (rectus femoris, vastus medialis, biceps femoris, tibialis anterior and gastrocnemius medialis) of both legs during pedaling. Two different methods of signal normalization were used for the data analysis. The first one normalized the data using the maximum value achieved by each muscle. The second one was based on the maximum voluntary contraction (MVC) test that was recorded during each session. All the six healthy subjects that underwent to the pedaling test were able to obtain an MVC level over the activation reached by each muscles during the pedaling exercise. Their results assessed that biceps femoris, tibialis anterior and gastrocnemius medialis had a low activation level (peak value at 8%, 14% and 15% respectively). Concerning the tibialis and the gastrocnemius this could be explained as the subjects wore an ankle foot orthosis that fixed the ankle angle at  $90^\circ$ . Moreover the action of the BF and of the distal muscles on the pedaling movement is more relevant in subject trained in pedaling (e.g. professional cyclist), while the subject tested were not exercised. Finally previous studies assessed that during pedaling the most active muscular group is the quadriceps [56].

Two out of four patients were able to perform the MVC test properly for all the muscles during all the assessment tests. Thus only the results of these two patients was normalized to MVC obtaining information on both the activation timing and the level of activation of each muscles with respect to its maximum activation.

The results showed slight improvements only in the most proximal muscles (rectus femoris, vastus medialis and biceps femoris). In particular one of the subject slightly improved the activation timing for all this three muscles in the POST test, but the results were not maintained at FU. Another subject maintained substantially unvaried the activation timing of this three muscles, although some of them were slightly impaired. The other two subjects did not present a coherent trend of improvements over time.

Concerning the distal muscles few observations could be gained because, similarly to the healthy subjects' results, a great variability of the data intra-session was observed affecting the reliability of the EMG profiles of tibialis anterior and gastrocnemius medialis.

Last outcome of the pedaling test was an index of the co-contraction between a couple of agonist-antagonist muscles: the RF and the BF. Two out of four patients showed a correct synergy between the two muscles already at baseline, that was maintained over time. One patient presented value during the PRE session of the paretic limb significantly different from the control group while after the treatment an improvement was obtained. The last patients presented an exaggerated overlap between the profiles of the two muscles of paretic leg, that he maintained over time.

Thus, summarizing the results of the EMG analysis, no unequivocal improvement in term of activation timing was shown.

During the pedaling test was observed that the results between oPRE and PRE test were not always similar. While the repeatability of the activation timing in cycling for healthy adult subjects was already confirmed (shifted onset and offset within the 15° in different sessions) in literature [56], no research investigated this on young subjects. Further studies could be carried out on both healthy and impaired young population assessing the repeatability of work, muscular activation level and timing during pedaling.

In conclusion, the four recruited patients were slightly impaired at baseline. The clinical assessment did not highlight severe deficits in none of the scales used while only few deviations in gait analysis and in the activation timing of the muscles during cycling exercise were observed before the training. A 7-week FES-augmented volitional cycling treatment gave some evidence that the treatment improved ROM and propulsive power of distal muscles during the gait while a greater symmetry was shown for some of the patients.

The improvement were not always imputable to the training as the study design allowed



to assess that the size of the variability between oPRE and PRE sessions was often similar to the variation achieved between baseline and POST test. In the future, a systematic evaluation of intra-session repeatability of both gait analysis and pedaling test on young hemiparetic subjects could be carried out in order to better understand the significance of the results.

The study supported the feasibility of the FES-cycling treatment of young hemiparetic thus the results could be extended in future work recruiting subjects affected by more severe disability. Moreover further studies could be carried out including a bigger sample size hemiparetic subjects as only few studies are focused on young population.

As the study was aimed at enhancing the neuroplasticity, some interesting investigation could be also addressed to the assessment of neuroplasticity changes on this young subjects with transcranial magnetic stimulation or imaging technique.

The comparison of results with a standard cycling training could also be required in order to assess the amount of variation that can be ascribed to the FES.

# Bibliography

- [1] VM Pomeroy, L King, A Pollock, A Baily-Hallam, and P Langhorne. Electrostimulation for promoting recovery of movement or functional ability after stroke. *Cochrane Database Syst Rev*, 2, 2006.
- [2] Regina M Crameri, Philip Cooper, Peter J Sinclair, Grace Bryant, and Adele Weston. Effect of load during electrical stimulation training in spinal cord injury. *Muscle & nerve*, 29(1):104–111, 2004.
- [3] Glen M Davis, Nur A Hamzaid, and Ché Fornusek. Cardiorespiratory, metabolic, and biomechanical responses during functional electrical stimulation leg exercise: health and fitness benefits. *Artificial organs*, 32(8):625–629, 2008.
- [4] DN Rushton. Functional electrical stimulation and rehabilitation—an hypothesis. *Medical engineering & physics*, 25(1):75–78, 2003.
- [5] R Benecke, B-U Meyer, and H-J Freund. Reorganisation of descending motor pathways in patients after hemispherectomy and severe hemispheric lesions demonstrated by magnetic brain stimulation. *Experimental Brain Research*, 83(2):419–426, 1991.
- [6] S Ferrante, BA Saunders, L Duffell, A Pedrocchi, K Hunt, T Perkins, and N Donaldson. Quantitative evaluation of stimulation patterns for fes cycling. In *Proceedings of 10th Annual Conference of the International FES Society, Montreal, Canada*, pages 94–96, 2005.
- [7] Philip A Wright, Sally Durham, David J Ewins, and Ian D Swain. Neuromuscular electrical stimulation for children with cerebral palsy: a review. *Archives of disease in childhood*, 97(4):364–371, 2012.

- 
- [8] Ann Tokay Harrington, Calum GA McRae, and Samuel CK Lee. Evaluation of functional electrical stimulation to assist cycling in four adolescents with spastic cerebral palsy. *International journal of pediatrics*, 2012, 2012.
- [9] E Trevisi, S Gualdi, C De Conti, A Salghetti, A Martinuzzi, Alessandra Pedrocchi, Simona Ferrante, et al. Cycling induced by functional electrical stimulation in children affected by cerebral palsy: case report. *European journal of physical and rehabilitation medicine*, 48(1):135–145, 2012.
- [10] Eileen G Fowler, Loretta M Knutson, Sharon K DeMuth, Kara L Siebert, Victoria D Simms, Mia H Sugi, Richard B Souza, Roksana Karim, Stanley P Azen, et al. Pediatric endurance and limb strengthening (pedals) for children with cerebral palsy using stationary cycling: a randomized controlled trial. *Physical therapy*, 90(3):367–381, 2010.
- [11] J K Tilson, K J Sullivan, S Y Cen, D K Rose, C H Koradia, S P Azen, and P W et al Duncan. Meaningful gait speed improvement during the first 60 days poststroke: minimal clinically important difference. *Physical Therapy*, 90(2):196–208, 2010.
- [12] M Sara Cuccurullo. *Physical medicine and rehabilitation board review*. Demos Medical Pub, 2004.
- [13] Frigo C. Fenomenologia della locomozione. 2012.
- [14] S J Olney and C Richards. Hemiparetic gait following stroke. part i: Characteristics. *Gait & Posture*, 4(2):136–148, 1996.
- [15] K Roeleveld, DF Stegeman, HM Vingerhoets, and A van Oosterom. The motor unit potential distribution over the skin surface and its use in estimating the motor unit location. *Acta physiologica scandinavica*, 161(4):465–472, 1997.
- [16] R N Boyd and H K Graham. Objective measurement of clinical findings in the use of botulinum toxin type a for the management of children with cerebral palsy. *European Journal of Neurology*, 6(S4):s23–s35, 1999.
- [17] Ruth Bonita and Robert Beaglehole. Recovery of motor function after stroke. *Stroke*, 19(12):1497–1500, 1988.

- [18] Giacomo Rizzolatti, Giuseppe Luppino, et al. The cortical motor system. *Neuron*, 31(6):889–902, 2001.
- [19] Ardiana Murtezani, Hajrie Hundozi, Valbona Krasniqi, Teuta Osmani, Bukurie Rama, et al. Epidemiologic and rehabilitation characteristics of hemiplegic patients treated during 2003–2008. *Journal of Chinese Clinical Medicine*, 4(10), 2009.
- [20] Gabrielle deVeber et al. Stroke and the child’s brain: an overview of epidemiology, syndromes and risk factors. *Current opinion in neurology*, 15(2):133–138, 2002.
- [21] Elizabeth Perkins, Julie Stephens, Huiyun Xiang, and Warren Lo. The cost of pediatric stroke acute care in the united states. *Stroke*, 40(8):2820–2827, 2009.
- [22] MPH John Kylan Lynch DO. Cerebrovascular disorders in children. *Current neurology and neuroscience reports*, 4(2):129–138, 2004.
- [23] M Bax, M Goldstein, P Rosenbaum, A Leviton, N Paneth, B Dan, B Jacobsson, and D Damiano. Proposed definition and classification of cerebral palsy, april 2005. *Developmental Medicine & Child Neurology*, 47(08):571–576, 2005.
- [24] Chitra Sankar and Nandini Mundkur. Cerebral palsy-definition, classification, etiology and early diagnosis. *The Indian Journal of Pediatrics*, 72(10):865–868, 2005.
- [25] Christine Cans. Surveillance of cerebral palsy in europe: a collaboration of cerebral palsy surveys and registers. *Developmental Medicine & Child Neurology*, 42(12):816–824, 2000.
- [26] E Biondi and C Cobelli. *Storia della bioingegneria*. Patron Editore, 2001.
- [27] WT Liberson, HJ Holmquest, et al. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Archives of physical medicine and rehabilitation*, 42:101, 1961.
- [28] L Vodovnik. Functional electrical stimulation of extremities. *Advances in Electronics and Electron Physics*, 30:283–297, 1971.
- [29] JT Mortimer. Motor prostheses. *Comprehensive Physiology*, 1981.

- [30] DN Rushton. Functional electrical stimulation. *Physiological measurement*, 18(4):241, 1997.
- [31] X Navarro, Krueger TB, N Lago, S Micera, T Stieglitz, and P Dario. A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems. *Journal of the Peripheral Nervous System*, 10(3):229–258, 2005.
- [32] Dejan Popovic, Tessa Gordon, Victor F Rafuse, and Arthur Prochazka. Properties of implanted electrodes for functional electrical stimulation. *Annals of biomedical engineering*, 19(3):303–316, 1991.
- [33] ER Kandel, JH Schwartz, TM Jessell, Virgilio Perri, and Giuseppe Spidalieri. *Principi di neuroscienze*. Cea, 2003.
- [34] FE Zajac and JS Faden. Relationship among recruitment order, axonal conduction velocity, and muscle-unit properties of type-identified motor units in cat plantaris muscle. *Journal of neurophysiology*, 53(5):1303–1322, 1985.
- [35] AJ Bergquist, JM Clair, O Lagerquist, CS Mang, Y Okuma, and DF Collins. Neuro-muscular electrical stimulation: implications of the electrically evoked sensory volley. *European journal of applied physiology*, 111(10):2409–2426, 2011.
- [36] S Trojan and J Pokorny. Theoretical aspects of neuroplasticity. *Physiological research*, 48:87–98, 1999.
- [37] H Mäenpää et al. *Electrostimulation therapy and selective posterior rhizotomy in the treatment of children with cerebral palsy*. University of Helsinki, 2005.
- [38] Nandini Mundkur. Neuroplasticity in children. *The Indian Journal of Pediatrics*, 72(10):855–857, 2005.
- [39] C Bütefisch, H Hummelsheim, P Denzler, and KH Mauritz. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. *Journal of the neurological sciences*, 130(1):59–68, 1995.

- 
- [40] LR Sheffler and J Chae. Neuromuscular electrical stimulation in neurorehabilitation. *Muscle & nerve*, 35(5):562–590, 2007.
- [41] TW Janssen, DD Pringle, et al. Effects of modified electrical stimulation-induced leg cycle ergometer training for individuals with spinal cord injury. *J Rehabil Res Dev*, 45(6):819–30, 2008.
- [42] Tiebin Yan, Christina WY Hui-Chan, and Leonard SW Li. Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke a randomized placebo-controlled trial. *Stroke*, 36(1):80–85, 2005.
- [43] G Alon, VM Conroy, and TW Donner. Intensive training of subjects with chronic hemiparesis on a motorized cycle combined with functional electrical stimulation (fes): A feasibility and safety study. *Physiotherapy Research International*, 16(2):81–91, 2011.
- [44] Judith M Burnfield, Yu Shu, Thad Buster, and Adam Taylor. Similarity of joint kinematics and muscle demands between elliptical training and walking: implications for practice. *Physical Therapy*, 90(2):289–305, 2010.
- [45] LD Duffell, NN Donaldson, and DJ Newham. Power output during functional electrically stimulated cycling in trained spinal cord injured people. *Neuromodulation: Technology at the Neural Interface*, 13(1):50–57, 2010.
- [46] C Fornusek, GM Davis, PJ Sinclair, and B Milthorpe. Development of an isokinetic functional electrical stimulation cycle ergometer. *Neuromodulation: Technology at the Neural Interface*, 7(1):56–64, 2004.
- [47] A Seifart, M Unger, and M Burger. The effect of lower limb functional electrical stimulation on gait of children with cerebral palsy. *Pediatric Physical Therapy*, 21(1):23–30, 2009.
- [48] TA Perkins, N Donaldson, R Fitzwater, GF Phillips, DE Wood, W Mayr, M Bijak, and C Jancik. Leg powered paraplegic cycling system using surface functional electri-

- cal stimulation. *Department of Biomedical Engineering and Physics Univ of Vienna, Austria*, pages 36–39, 2001.
- [49] JS Petrofsky. New algorithm to control a cycle ergometer using electrical stimulation. *Medical and Biological Engineering and Computing*, 41(1):18–27, 2003.
- [50] S Ferrante, A Pedrocchi, G Ferrigno, and F Molteni. Minerva medica copyright. *European Journal of Physical and Rehabilitation Medicine*, 44:159–67, 2008.
- [51] E Ambrosini, S Ferrante, G Ferrigno, F Molteni, and A Pedrocchi. Cycling induced by electrical stimulation improves muscle activation and symmetry during pedaling in hemiparetic patients. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, 20(3):320–330, 2012.
- [52] AM Tokay, CG McRae, T Johnston, and SC Lee. The use of functional electrical stimulation assisted cycling in adolescents with cerebral palsy. *Biomedizinische Technik—Biomedical Engineering*, 53(supplement 1):376–378, 2008.
- [53] SR Simon. Quantification of human motion: gait analysis-benefits and limitations to its application to clinical problems. *Journal of Biomechanics*, 37(12):1869–1880, 2004.
- [54] R Merletti and P Parker. Physiology, engineering, and noninvasive applications. *Electromyography*, 2005.
- [55] R Merletti, M Knaflitz, C J De Luca, et al. Electrically evoked myoelectric signals. *Crit Rev Biomed Eng*, 19(4):293–340, 1992.
- [56] F Hug and S Dorel. Electromyographic analysis of pedaling: a review. *Journal of electromyography and kinesiology: official journal of the International Society of Electrophysiological Kinesiology*, 19(2):182, 2009.
- [57] D Denny-Brown. Interpretation of the electromyogram. *Archives of Neurology & Psychiatry*, 61(2):99–28, 1949.
- [58] JW Morrenhof and HJ Abbink. Cross-correlation and cross-talk in surface electromyography. *Electromyography and clinical neurophysiology*, 25(1):73, 1985.

- [59] CJ De Luca and R Merletti. Surface myoelectric signal cross-talk among muscles of the leg. *Electroencephalography and clinical Neurophysiology*, 69(6):568–575, 1988.
- [60] Hermie J Hermens, Bart Freriks, Roberto Merletti, Dick Stegeman, Joleen Blok, Günter Rau, Cathy Disselhorst-Klug, and Göran Hägg. *European recommendations for surface electromyography*. Roessingh Research and Development The Netherlands, 1999.
- [61] Evert Knutsson, Carol Richards, et al. Different types of disturbed motor control in gait of hemiparetic patients. *Brain: a journal of neurology*, 102(2):405, 1979.
- [62] SA Kautz and DA Brown. Relationships between timing of muscle excitation and impaired motor performance during cyclical lower extremity movement in post-stroke hemiplegia. *Brain*, 121(3):515–526, 1998.
- [63] R W Bohannon and M B Smith. Interrater reliability of a modified ashworth scale of muscle spasticity. *Physical therapy*, 67(2):206–207, 1987.
- [64] T F Winters, JR Gage, and R Hicks. Gait patterns in spastic hemiplegia in children and young adults. *J Bone Joint Surg Am*, 69(3):437–441, 1987.
- [65] Dianne J Russell, Peter L Rosenbaum, David T Cadman, Carolyn Gowland, Susan Hardy, and Sheila Jarvis. The gross motor function measure: a means to evaluate the effects of physical therapy. *Developmental Medicine & Child Neurology*, 31(3):341–352, 1989.
- [66] D J Russell, L M Avery, P L Rosenbaum, P S Raina, S D Walter, and R J Palisano. Improved scaling of the gross motor function measure for children with cerebral palsy: evidence of reliability and validity. *Physical Therapy*, 80(9):873–885, 2000.
- [67] J Szecsi and M Schiller. Fes-propelled cycling of sci subjects with highly spastic leg musculature. *NeuroRehabilitation*, 24(3):243–253, 2009.
- [68] Roy B Davis, Sylvia Ounpuu, Dennis Tyburski, and James R Gage. A gait analysis data collection and reduction technique. *Human Movement Science*, 10(5):575–587, 1991.



- [69] Frigo C. L'analisi strumentale del cammino. 2008.
- [70] L Comolli, S Ferrante, A Pedrocchi, M Bocciolone, G Ferrigno, and F Molteni. Metrological characterization of a cycle-ergometer to optimize the cycling induced by functional electrical stimulation on patients with stroke. *Medical engineering & physics*, 32(4):339–348, 2010.
- [71] Gerhardt Steinwender, Vinay Saraph, Sabine Scheiber, Ernst Bernhard Zwick, Christiane Uitz, Karl Hackl, et al. Intrasubject repeatability of gait analysis data in normal and spastic children. *Clinical biomechanics (Bristol, Avon)*, 15(2):134, 2000.