Universidad de Alcalá
COMISIÓN DE ESTUDIOS OFICIALES DE POSGRADO Y DOCTORADO

ACTA DE EVALUACIÓN DE LA TESIS DOCTORAL

Año académico 2016/17

DOCTORANDO: **TRINCADO ALONSO, FERNANDO**
D.N.I./PASAPORTE: ******5227Z**

PROGRAMA DE DOCTORADO: **D332 DOCTORADO EN ELECTRÓNICA:SISTEMAS ELECTRÓNICOS AVANZADOS.SISTEMAS INTELIGEN**
DEPARTAMENTO DE: **Electrónica**
TITULACIÓN DE DOCTOR EN: **DOCTOR/A POR LA UNIVERSIDAD DE ALCALÁ**

En el día de hoy 11/07/17, reunido el tribunal de evaluación nombrado por la Comisión de Estudios Oficiales de Posgrado y Doctorado de la Universidad y constituido por los miembros que suscriben la presente Acta, el aspirante defendió su Tesis Doctoral, elaborada bajo la dirección de SIRA ELENA PALAZUELOS CAGIGAS // ÁNGEL MANUEL GIL AGUDO/ Mª DOLORES CASTILLO SOBRINO.

Sobre el siguiente tema: *FUSION OF VIRTUAL REALITY AND BRAIN-MACHINE INTERFACES FOR THE ASSESSMENT AND REHABILITATION OF PATIENTS WITH SPINAL CORD INJURY*

Finalizada la defensa y discusión de la tesis, el tribunal acordó otorgar la CALIFICACIÓN GLOBAL[9] de (**no apto, aprobado, notable** y **sobresaliente**): SOBRESALIENTE

Alcalá de Henares, 11 de julio de 2017

EL PRESIDENTE	EL SECRETARIO	EL VOCAL
Fdo.: S. L. Pons	Fdo.: L. Boquete	Fdo.: E. López-Dolado

Con fecha 24 de julio de 2017 la Comisión Delegada de la Comisión de Estudios Oficiales de Posgrado, a la vista de los votos emitidos de manera anónima por el tribunal que ha juzgado la tesis, resuelve:

- [X] Conceder la Mención de "Cum Laude"
- [ ] No conceder la Mención de "Cum Laude"

La Secretaria de la Comisión Delegada

FIRMA DEL ALUMNO,

Fdo.: F. Trincado

[9] La calificación podrá ser **"no apto" "aprobado" "notable"** y **"sobresaliente"**. El tribunal podrá otorgar la mención de "cum laude" si la calificación global es de sobresaliente y se emite en tal sentido el voto secreto positivo por unanimidad.

INCIDENCIAS / OBSERVACIONES:

Universidad de Alcalá
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En aplicación del art. 14.7 del RD. 99/2011 y el art. 14 del Reglamento de Elaboración, Autorización y Defensa de la Tesis Doctoral, la Comisión Delegada de la Comisión de Estudios Oficiales de Posgrado y Doctorado, en sesión pública de fecha 24 de julio, procedió al escrutinio de los votos emitidos por los miembros del tribunal de la tesis defendida por *TRINCADO ALONSO, FERNANDO*, el día 11 de julio de 2017, titulada *FUSION OF VIRTUAL REALITY AND BRAIN-MACHINE INTERFACES FOR THE ASSESSMENT AND REHABILITATION OF PATIENTS WITH SPINAL CORD INJURY*, para determinar, si a la misma, se le concede la mención "cum laude", arrojando como resultado el voto favorable de todos los miembros del tribunal.

Por lo tanto, la Comisión de Estudios Oficiales de Posgrado **resuelve otorgar** a dicha tesis la

MENCIÓN "CUM LAUDE"

Alcalá de Henares, 27 julio de 2017
EL PRESIDENTE DE LA COMISIÓN DE ESTUDIOS
OFICIALES DE POSGRADO Y DOCTORADO

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Juan Ramón Velasco Pérez

Copia por e-mail a:
Doctorando: TRINCADO ALONSO, FERNANDO
Secretario del Tribunal: LUCIANO BOQUETE VÁZQUEZ.
Directores de Tesis: SIRA ELENA PALAZUELOS CAGIGAS // ÁNGEL MANUEL GIL AGUDO/ Mª DOLORES CASTILLO SOBRINO

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DILIGENCIA DE DEPÓSITO DE TESIS.

Comprobado que el expediente académico de D./Dª FERNANDO TRINCADO ALONSO reúne los requisitos exigidos para la presentación de la Tesis, de acuerdo a la normativa vigente, y habiendo presentado la misma en formato: ☒ soporte electrónico ☐ impreso en papel, para el depósito de la misma, en el Servicio de Estudios Oficiales de Posgrado, con el nº de páginas: 139 se procede, con fecha de hoy a registrar el depósito de la tesis.

Alcalá de Henares a 26 de ABRIL de 2017

UNIVERSIDAD DE ALCALÁ
SERVICIO DE ESTUDIOS OFICIALES DE POSGRADO

Rosa Carrillo Salas

Fdo. El Funcionario

PhD. Program in Electronics: Advanced Electronic Systems. Intelligent Systems

FUSION OF VIRTUAL REALITY AND BRAIN-MACHINE INTERFACES FOR THE ASSESSMENT AND REHABILITATION OF PATIENTS WITH SPINAL CORD INJURY

PhD Thesis Presented by

FERNANDO TRINCADO ALONSO

2017

PhD. Program in Electronics: Advanced Electronic Systems. Intelligent Systems

FUSION OF VIRTUAL REALITY AND BRAIN-MACHINE INTERFACES FOR THE ASSESSMENT AND REHABILITATION OF PATIENTS WITH SPINAL CORD INJURY

Advisors:

DRA. SIRA ELENA PALAZUELOS CAGIGAS

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Alcalá de Henares, 2017

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Dra. Dª Mª Dolores del Castillo Sobrino, científica titular del Consejo Superior de Investigaciones Científicas

INFORMAN: que la Tesis Doctoral titulada **Fusion of virtual reality and brain-machine interfaces for the assessment and rehabilitation of patients with spinal cord injury**, presentada por D. **Fernando Trincado Alonso**, y realizada bajo nuestra dirección, dentro del campo de la tecnología aplicada a la rehabilitación, reúne los méritos de calidad y originalidad para optar al Grado de Doctor.

Alcalá de Henares a 25 de abril de 2017,

UNIVERSIDAD DE ALCALÁ * DEPARTAMENTO DE ELECTRÓNICA * EDIFICIO POLITÉCNICO

Fdo.: Sira E. Palazuelos Cagigas | Angel M. Gil Agudo | Mª Dolores del Castillo Sobrino

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Dra. Sira Elena Palazuelos Cagigas, Directora del Departamento de Electrónica de la Universidad de Alcalá,

INFORMA: Que la Tesis Doctoral titulada **"Fusion of virtual reality and brain-machine interfaces for the assessment and rehabilitation of patients with spinal cord injury"** presentada por D. **Fernando Trincado Alonso**, y dirigida por los doctores D.ª Sira E. Palazuelos Cagigas, D. Angel M. Gil Agudo y D.ª Mª Dolores del Castillo Sobrino, reúne los requisitos científicos de originalidad y rigor metodológicos para ser defendida ante un tribunal.

Para que así conste y surta los efectos oportunos, se firma el presente informe en Alcalá de Henares, 24 abril de 2017

UNIVERSIDAD DE ALCALÁ
DEPARTAMENTO DE ELECTRÓNICA
EDIFICIO POLITÉCNICO

Fdo. Sira Elena Palazuelos Cagigas

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Index of acronyms

ACC: Anterior Cingulate Cortex
ADL: Activities of Daily Living
AR: Autorregresive
ARAT: Action Research Arm Test
ASIA: American Spinal Injury Association
BMI: Brain-Machine Interface
CAR: Common Average Reference
CI: Constraint-Induced
CMI: Cross-Mutual Information
CSD: Current Source Density
DCM: Dynamic Causal Modeling
DoF: Degrees of Freedom
DTF: Directed Transfer Function
EC: Effective Connectivity
EEG: Electroencephalographic
ERD: Event-Related Desynchronization
FC: Functional Connectivity
FES: Functional Electrical Stimulator
FFT: Fast-Fourier Transform
FIM: Functional Independence Measure
FMA: Fugl-Meyer Assessment
fMRI: functional magnetic resonance imaging
GC: Granger Causality
GRASSP: Graded and Redefined Assessment of Strength, Sensibility and Prehension
GS: Generalized Synchronization
GSYM: Global Synchrony Metric
HLC: High-Level Controller
IC: Imaginary Part of Coherence
ICC: Intra-Class Correlation
IMU: Inertial Measurement Unit
IPL: Inferior Parietal Lobe
iSCI: incomplete Spinal Cord Injury
LDA: Linear Discriminant Analysis
LTP: Long-Term Potentiation
MA: Motot Attempt
MAL: Motor Activity Log
MDL: Minimum Description Length
MI: Motricity Index
MMT: Manual Muscle Testing
MRCP: Movement-Related Cortical Potential
MSC: Magnitude Squared Coherence
NLI: Neurological Level of Injury
PDC: Partial-Directed Coherence
PLI: Phase-Lag Index
PLV: Phase-locking Value
PMC: Premotor Cortex
PSD: Power Spectral Density
ROM: Range of Motion
SCI: Spinal Cord Injury

SCIM: Spinal Cord Independence Measure
SDA: Sparse Discriminant Analysis
SEM: Structural Equation Modeling
SL: Surface Laplacian
SMA: Supplementary Motor Area
TE: Transfer Entropy
UL: Upper Limb
VC: Volume Conduction
VR: Virtual Reality
WC: Wavelet Coherence
WPLI: Weighted version of Phase-Lag Index

Agradecimientos

Esta tesis se la dedico fundamentalmente a aquellos que me apoyan diariamente a seguir en el mundo investigador, tan complicado a veces, pero tan gratificante la mayor parte del tiempo. Por supuesto a Nalli, porque es mi inspiración y porque si ella no se sintiese orgullosa de mí no tendría tanta ilusión en el día a día. A mi familia: mis padres, que siempre me han despertado la curiosidad y el gusto por el estudio y el conocimiento, mis abuelas Marga y Nena, que fue la primera que me vio al nacer, jejeje. A mis hermanos, Sofía y Babí, que ahora es también hermano de la investigación en "biocosas". A mis amigos de la Prospe, porque me han picado con eso de los doctorados. A mis compañeros de Biomecánica del Hospital de Parapléjicos, donde he pasado 4 años magníficos, disfrutando día a día el inmenso placer de poder trabajar en algo que te apasiona. Aunque ahora nuestros caminos se han separado, no me cabe duda que volveremos a encontrarnos en el futuro. También a Eduardo, mi compañero de fatigas en los experimentos, y con el que he compartido muchas charlas científicas.

Como no, agradecer a mis directores de tesis su buena disposición, sus ideas y sus ánimos en los momentos de más agobio.

No podría olvidarme, como no, de los pacientes con lesión medular, los principales motivos por los que se ha realizado esta tesis. Por un lado, por su colaboración en estos estudios, en los que han tenido la paciencia de participar en los experimentos, y por otro lado, y fundamentalmente, por su ejemplo de vida y su motivación. Para mí ha sido una gran experiencia poder conocer a personas como Alejandro, Mohamed, Mº José, etc.; compartir con ellos parte de sus vidas, sus experiencias, sus ganas y motivación de seguir adelante a pesar de lo que les ha tocado vivir… Ellos han sido el principal motor de esta tesis, y todos los esfuerzos encaminados al desarrollo de tecnologías que puedan, aunque sólo sea un poco, ayudarles en su día a día, se quedan cortos.

Espero que esta tesis no sea un punto final, sino un punto y seguido en la tarea de hacer tecnologías al servicio de las personas, y no personas al servicio de las tecnologías.

RESUMEN

1. Introducción

La presente tesis está centrada en la utilización de nuevas tecnologías (Interfaces Cerebro-Máquina y Realidad Virtual). La tesis consta de 3 estudios descritos en los capítulos 2, 3 y 4, junto con un capítulo introductorio (Capítulo 1) y un capítulo final (Capítulo 5) que resume las principales conclusiones y los trabajos de cara a futuro. En cada estudio se ha descrito un estado del arte, una metodología, unos resultados, una discusión y unas conclusiones.

En la primera parte de la tesis (capítulo 2) se describe la definición y la aplicación de un conjunto de métricas para evaluar el estado funcional de los pacientes con lesión medular en el contexto de un sistema de realidad virtual para la rehabilitación de los miembros superiores. El objetivo de este primer estudio es demostrar que la realidad virtual puede utilizarse, en combinación con sensores inerciales para rehabilitar y evaluar simultáneamente. 15 pacientes con lesión medular llevaron a cabo 3 sesiones con el sistema de realidad virtual Toyra y se aplicó el conjunto definido de métricas a las grabaciones obtenidas con los sensores inerciales. Se encontraron correlaciones entre algunas de las métricas definidas y algunas de las escalas clínicas utilizadas con frecuencia en el contexto de la rehabilitación.

La rehabilitación con Toyra se centró en los pacientes con un cierto grado de movilidad en los miembros superiores. Sin embargo, el uso de realidad virtual para la rehabilitación no se limita a este tipo de pacientes. También existe la posibilidad de ejercer la rehabilitación incluso en los casos más graves. El campo de las Interfaces Cerebro-Máquina (en adelante BMI por sus siglas en inglés-Brain Machine Interface-) abrió la puerta a un nuevo paradigma de rehabilitación, en el que los movimientos son ordenados desde la propia intención del paciente, a través de sus señales electroencefalográficas (EEG). Esto permite la introducción de realidad virtual en la rehabilitación de pacientes que no son capaces de mover sus extremidades. En la segunda parte de la tesis (capítulo 3), hemos combinado una retroalimentación virtual con un estimulador eléctrico funcional (en adelante FES, por sus siglas en inglés-Functional Electrical Stimulator-), ambos controlados por un BMI, para desarrollar un nuevo tipo de enfoque terapéutico para los pacientes. El sistema ha sido utilizado por 4 pacientes con lesión medular que intentaron mover sus manos. Esta intención desencadenó simultáneamente el FES y la retroalimentación virtual, cerrando la mano de los pacientes y mostrándoles una fuente adicional de retroalimentación para complementar la terapia. La realidad puede servir para superar una de las limitaciones del FES, que es que la mano del paciente no siempre reacciona a la corriente eléctrica de la misma manera, y, por lo tanto, a veces la mano se cierra con diferentes patrones. Al mostrar la mano virtual que siempre se cierra correctamente, siempre podemos proporcionar al paciente una retroalimentación positiva, independientemente de la respuesta de su miembro a la estimulación eléctrica. Por otra parte, la realidad virtual podría ofrecer una recompensa adicional a la terapia, mediante el suministro de objetos virtuales con el fin de realizar tareas dirigidas a objetivos.

Este trabajo es, de acuerdo al estado del arte revisado, el primero que integra BMI, FES y realidad virtual como terapia para pacientes con lesión medular. Se han obtenido resultados clínicos prometedores por 4 pacientes con lesión medular después de realizar 5 sesiones de terapia con el sistema, mostrando buenos niveles de precisión en las diferentes sesiones (79,13% en promedio).

Ambos sistemas (Toyra y BMI + FES + VR) ya descritos en las dos primeras partes de la tesis han sido diseñados con el propósito de promover neuroplasticidad, que podría definirse como el proceso que experimenta el sistema nervioso central para restaurar y reparar las áreas que han sido dañadas por una lesión, como la lesión medular. Con el fin de evaluar la eficacia de las nuevas tecnologías para la neurorrehabilitación, el abordaje más habitual suele ser medir los efectos en el estado físico de los pacientes, como lo hemos hecho en la primera parte de la tesis con las métricas cinemáticas definidas. Sin embargo, la recuperación neurológica suele preceder a la recuperación funcional. Por lo tanto, también es importante estudiar los cambios en la actividad neuronal de los pacientes después de realizar una terapia.

Existen muchas técnicas diferentes para medir las interacciones cerebrales, muchas de ellas basadas en señales de resonancia magnética funcional (fMRI por sus siglas en inglés- Functional Magnetic Resonance Imaging). Por otro lado, el electroencefalograma (EEG) ofrece una alternativa interesante para el desarrollo de las tecnologías de neurorrehabilitación, ya que es portátil y más barato que fMRI. Además, tiene una mejor resolución temporal, por lo que permite estudiar de manera precisa las interacciones temporales entre diferentes áreas del cerebro. En la tercera parte (capítulo 4) de la tesis hemos definido una nueva métrica para estudiar los cambios de conectividad cerebral en los pacientes con lesión medular, que comprende información de las interacciones neuronales entre diferentes áreas. El objetivo de este estudio ha sido extraer información clínicamente relevante de la actividad del EEG cuando se realizan terapias basadas en BMI (con FES + VR en un estudio y con exoesqueleto en otro). El objetivo ha sido desarrollar nuevos enfoques para medir si las nuevas tecnologías de neurorrehabilitación (BMI, VR, exoesqueletos) han promovido efectivamente la neuroplasticidad.

2. Antecedentes

2.1 Métricas cinemáticas

La cuantificación de los movimientos de las extremidades superiores se ha investigado durante muchos años. Uno de los primeros estudios en este campo fue llevado a cabo por Fitts en 1954 con el objetivo de analizar el equilibrio velocidad-exactitud y, en consecuencia, calcular el rendimiento y un índice de dificultad de una tarea a partir de tres parámetros: el tiempo dedicado a realizar el movimiento, la distancia y el tamaño del objeto a alcanzar [1].

El interés en obtener parámetros que pudieran proporcionar información relevante para el personal clínico a partir de la cuantificación de los movimientos de las extremidades superiores es relativamente reciente. Existen algunos estudios que analizan los movimientos realizados por los pacientes con trastornos neurológicos durante la realización de las tareas y también dibujando [2]–[4]. También hay estudios en los que se ha analizado una actividad básica de la vida diaria (AVD), como la de beber, en personas con accidente cerebrovascular [5] o SCI [6], y también se han desarrollado algunas métricas para una tarea específica [7], [8].

En la mayoría de los estudios mencionados, se han utilizado sistemas de fotogrametría para registrar la información de movimiento, que son el estándar más utilizado para el análisis biomecánico, debido a su precisión. Por el contrario, en este trabajo, hemos extraído información de los sensores inerciales, ya que permiten diseñar sistemas para ser utilizados fuera del entorno de un laboratorio de análisis de movimiento, ya que no requieren cámaras adicionales para capturar los movimientos. Esto es de especial interés para el desarrollo de sistemas de realidad virtual para la rehabilitación. Por otra parte, muchos de los estudios anteriores se centraron en una tarea específica, pero estamos más interesados en métricas que puedan incluir muchos movimientos diferentes en un solo valor, para ofrecer una medición global que podría estar relacionada con la funcionalidad. Existe aún la necesidad de investigar en mayor profundidad la validez de este tipo de métricas en un entorno clínico [9], por lo tanto, creemos que es necesario buscar relaciones entre los parámetros clínicos y métricas cinemáticas.

2.2 BMI en rehabilitación de los miembros superiores

Las interfaces cerebro-máquina (BMI) permiten la decodificación en tiempo real de los comandos neuronales (por ejemplo, mediante el uso de señales electroencefalográficas), y por lo tanto, proporcionan un método muy útil para detectar intención de movimento. La intención del paciente se identifica a partir de la actividad neural en curso y se puede utilizar para controlar diferentes dispositivos. Este enfoque abrió la puerta a varias aplicaciones de BMI que podrían ser utilizadas potencialmente por pacientes con lesión medular completa, la mayoría de ellos con fines asistivos. Sin embargo, el potencial del BMI para la rehabilitación es especialmente relevante en pacientes con lesión medular incompleta, ya que se cree que el mantenimiento de tan sólo el 10% de las vías neuronales es suficiente para proporcionar una recuperación funcional [10].

La combinación de BMI y FES se puede utilizar con un propósito de rehabilitación en la lesión incompleta de médula espinal [11], basándose en la hipótesis de que una potenciación a largo plazo (LTP, por sus siglas en inglés-Long Term Potentiation) se induce en las sinapsis en la médula espinal cuando las señales descendentes del cerebro alcanzan la sinapsis aproximadamente al mismo tiempo que los impulsos antidrómicos de los nervios periféricos estimulados [12]. Desde esta perspectiva y apoyado por el principio del aprendizaje hebbiano [13], una terapia basada en la activación simultánea de las vías motoras (a través de la intención motora detectada por el BMI) y las vías sensoriales (a través de la estimulación eléctrica funcional) del tracto corticoespinal debe tener un efecto mayor que ambas terapias por separado [14].

Por otra parte, como justificación de muchas terapias motoras existentes se establece la premisa de que la práctica repetitiva y atractiva utilizando el miembro afectado induce cambios plásticos en las redes neuronales implicadas en el control motor y el aprendizaje [15]. En este sentido, la retroalimentación es una característica clave durante la terapia de rehabilitación, ya que permite que los pacientes sientan sus mejoras de rendimiento a lo largo de las sesiones, por lo que los involucra y motiva, y también permite recibir una respuesta congruente con la intención motora. Sin embargo, las estructuras musculoesqueléticas humanas forman un sistema muy complejo que presenta respuestas musculares no lineales y variables al FES [16]. Por lo tanto, los pacientes tienen diferentes respuestas musculares a valores constantes de FES, dificultando la recepción de un feedback repetitivo y positivo durante la terapia. Esto puede compensarse mediante la inclusión de una fuente suplementaria de retroalimentación. El uso de una retroalimentación con realidad virtual permite la incorporación de una recompensa adicional, basada en los principios de juego para la rehabilitación, lo que puede mejorar la adhesión del paciente a la terapia [17]. Además, se ha planteado la hipótesis de que, dado que hay una mayor proporción de fibras visuales que entran en las estructuras cerebrales responsables del aprendizaje, la retroalimentación visual puede conducir a un aprendizaje más rápido [18]. De hecho, hay un estudio reciente que mostró recuperación significativa de la locomoción en pacientes con lesión medular después de 12 meses de entrenamiento con una combinación de BMI, exoesqueletos y realimentación de la realidad virtual [19].

Los BMI en combinación con FES y realidad virtual también ofrecen la posibilidad de evaluar el progreso del paciente durante el proceso de rehabilitación. Esto se puede lograr analizando las señales EEG grabadas durante las sesiones y con algoritmos de cálculo para medir la conectividad funcional (FC, por sus siglas en inglés-Functional Connectivity). Este tema se tratará durante el Capítulo 4 y, por lo tanto, no se explicará en este capítulo, pero es importante tenerlo en cuenta, porque este objetivo también estuvo presente durante el diseño del sistema.

Existen bastantes estudios apoyando los beneficios de los sistemas desencadenados por comandos neurofisiológicos para promover la recuperación motora en pacientes con ictus [20]–[22], así como la neuroplasticidad en sujetos sanos [23]. Sin embargo, hay menos estudios que aplican estos sistemas a pacientes con lesión medular. En un estudio reciente, BMI + FES se aplicó a pacientes con SCI completas e incompletas (ASIA [24] A y B, respectivamente) con un objetivo rehabilitador, obteniendo mejoras moderadas en los resultados funcionales del paciente con ASIA B y sin cambios en el paciente con ASIA A [25]. En otro estudio, BMI + FES se aplicaron para recuperar parcialmente la función de la marcha en un paciente con SCI [26]. Más recientemente, un estudio con pacientes con SCI ha demostrado que el BMI + FES restablece la actividad cortical y la fuerza muscular de la desincronización relacionada con el evento (ERD por sus siglas en inglés-Event Related Desynchronization) en mayor medida que el FES pasivo [27]. La combinación de BMI y exoesqueleto para la rehabilitación de miembros inferiores también se ha probado en pacientes con lesión medular [28]. Sin embargo, no está claro si el entrenamiento con BMI + FES puede inducir ganancias funcionales, por ello, en nuestro estudio se evalúa el estado funcional antes y después del entrenamiento mediante escalas clínicas.

Por todas estas razones, creemos que la integración de las tecnologías mencionadas en un único sistema, fácil de usar y seguro para los pacientes, es esencial para llenar el vacío existente entre los estudios de investigación y los estudios clínicos en el campo de los BMI. Antes de llegar a un estudio clínico para evaluar la efectividad de una terapia basada en tecnología, es fundamental llevar a cabo una evaluación piloto del sistema en un entorno clínico real, con el fin de probar el rendimiento del sistema y sus efectos inmediatos sobre los pacientes. Por lo tanto, el objetivo del presente trabajo es investigar si el sistema de retroalimentación en bucle cerrado resultante de la integración de BMI, FES y retroalimentación de la realidad virtual puede ser utilizado para la rehabilitación de la mano por parte de pacientes con SCI, en un entorno clínico, seguro y cómodo para la paciente. Con este fin, el primer paso fue diseñar un sistema que cumpliera todos los requisitos que se explicarán más detalladamente en la sección Métodos. Luego, se probó un sistema piloto inicial con 3 sujetos sanos para refinar las características, especialmente las relativas al clasificador de EEG. Después de redefinir el sistema y comprobar su buen desempeño con sujetos sanos, se realizó una experiencia piloto preclínica con 4 pacientes con SCI para evaluar la viabilidad del sistema en un entorno clínico.

2.3 Métricas de neuroplasticidad

En primer lugar, es necesario revisar los diferentes métodos que se han utilizado para determinar la conectividad en EEG, teniendo en cuenta sus ventajas y limitaciones. Es importante comenzar a distinguir entre 2 términos: conectividad funcional (FC) y conectividad efectiva (EC). El primer término se refiere a las correlaciones simétricas y no dirigidas entre la actividad de fuentes corticales, mientras que el segundo se refiere a dependencias dirigidas o causales [29]. Los primeros estudios calcularon FC a través de correlaciones lineales y coherencias entre señales EEG del cuero cabelludo [30], [31]. Estas técnicas presentan un grave riesgo de identificación errónea en sistemas con ruido correlacionado o fuerte autocorrelación, como es el caso de las señales cerebrales [32]. A pesar de esto, ambas están entre las herramientas más utilizadas para evaluar la conectividad en el campo de la neurociencia [33]. Algunos ejemplos de técnicas de EC son el modelado causal dinámico (DCM), la función de transferencia dirigida (DTF), el modelado de ecuaciones estructurales (SEM), la entropía de transferencia (TE) y el método de causalidad de Granger (GC). Una división de estas técnicas en 2 grupos (basada en modelos o basada en datos) se dará en las siguientes líneas, junto con una breve descripción de cada uno:

- Conectividad efectiva basada en modelos: estas técnicas utilizan modelos teóricos inspirados en la neurobiología. DCM y SEM se encuentran dentro de este grupo.
- Conectividad efectiva basada en datos: no asumen ningún modelo subyacente ni conocimientos previos sobre las relaciones espaciales o temporales subyacentes [33]. GC, DTF y coherencia parcialmente dirigida (PDC) se encuentran dentro de este grupo.

Con respecto a la conectividad funcional (FC), se puede establecer una división entre técnicas lineales, no lineales y basadas en información.

- Conectividad lineal: correlación cruzada, coherencia de magnitud al cuadrado (MSC), coherencia wavelet (WC) y parte imaginaria de coherencia (IC) se encuentran dentro de este grupo.
- Conectividad no lineal: estas métricas no están diseñadas para superar los métodos lineales, sino para dar cuenta de fenómenos no lineales que son fundamentales en el sistema neural, como la regulación de los canales iónicos de voltaje, que depende de una relación no lineal entre el potencial de membrana y el flujo de corriente [33]. Las técnicas de conectividad no lineal se basan en la medición de la sincronización. Existen principalmente 4 métodos diferentes para calcular la sincronización: valor de bloqueo de fase (PLV), sincronización generalizada (GS), índice de retardo de fase (PLI) e índice de retardo de fase ponderado (WPLI).
- Conectividad basada en la información: estas técnicas son capaces de detectar interacciones tanto lineales como no lineales. La información mutua cruzada (CMI), la longitud mínima de descripción (MDL) y la entropía de transferencia (TE) se encuentran dentro de esta categoría.

No hay una métrica de conectividad ideal; su adecuación depende de los fenómenos particulares o de la población estudiada. La sensibilidad a más aspectos de la dinámica neural puede ser una propiedad deseable, pero, al mismo tiempo, puede hacer que la métrica sea menos robusta [34]. Con respecto a la distinción entre métricas lineales y no lineales, es cuestionable que los métodos no lineales sean superiores a los lineales, a menos que la no linealidad sea el objetivo específico del estudio [34].

Estudios anteriores han reunido información sobre los cambios derivados de la neuroplasticidad a partir de EEG. De Vico et al. analizaron la conectividad funcional mediante la comparación de 5 sanos y 5 pacientes con SCI [35]. Otro estudio de Hou et al. analizaron mediante fMRI los patrones de conectividad de los sujetos con SCI en comparación con controles sanos. Obtuvieron hallazgos interesantes, como el aumento de FC intrahemisférico y disminuido entre hemisferios en pacientes con lesión medular en comparación con controles sanos. Encontraron que la FC entre la corteza sensorimotora primaria izquierda y el cerebelo izquierdo se incrementó en pacientes con lesión medular, y ésta FC se correlacionó negativamente con la puntuación motora del ASIA. También hallaron que la FC entre la corteza sensoriomotora primaria derecha y la SMA derecha estaba aumentado en los pacientes con SCI y también se correlacionaba negativamente con la puntuación motora del ASIA [36].

En otro estudio, Young et al. hallaron en pacientes con ictus después de realizar una terapia de neurofeedback mediada por BCI, algunas correlaciones entre cambios en escalas clínicas y cambios de FC entre diferentes áreas, especialmente entre el tálamo y la corteza motora y entre el tálamo y el cerebelo [37]. Sin embargo, algunas de estas correlaciones fueron positivas y otras fueron negativas, lo que sugiere que los cambios de FC debidos a la reorganización cerebral pueden ser también maladaptativos, lo cual está en línea con otros estudios [38]. Por lo tanto, existe la necesidad de investigar más acerca de cuáles de estos cambios FC están directamente relacionados con la neuroplasticidad positiva, especialmente en los sujetos con lesión medular, ya que, según nuestro conocimiento, no hay estudios sobre los cambios en FC después de una terapia BCI en sujetos con dicha lesión.

3. Metodología

3.1 Estudio métricas cinemáticas (capítulo 2)

Para el proceso de captura cinemática, se ha utilizado un sistema de captura de movimiento basado en sensores inerciales MTx Xsens Company (Xsens Inc, Países Bajos). En esta aplicación, 5 sensores inerciales se localizaron en la cabeza, el tronco, el brazo, el antebrazo y la mano. Los sensores capturan los movimientos principales de la extremidad superior: flexión / extensión del hombro, abducción / aducción del hombro, rotación del hombro, flexión / extensión del codo, pronosupinación, flexión / extensión de la muñeca y desviación radial-cubital. Estos movimientos se traducen en tiempo real a un avatar que aparece en la pantalla en un entorno virtual llamado Toyra, específicamente diseñado para realizar tareas de rehabilitación de miembros superiores. Este sistema comprende dos tipos de sesiones:

• Sesiones de evaluación: diseñadas para medir los rangos movimiento de los miembros superiores mencionados. Durante ellos, se requiere que los pacientes alcancen sus amplitudes máximas, tocando las esferas que aparecen secuencialmente en la pantalla.

• Sesiones de actividades de la vida diaria (AVD): fueron diseñadas para simular AVDs como comer con una cuchara, lavar con una esponja o agarrar objetos diferentes.

Los sensores inerciales MTx incluyen acelerómetros de tres ejes, giroscopios y magnetómetros. Teniendo en cuenta que los sensores inerciales sólo proporcionan información de la orientación de cada segmento del cuerpo, se requiere un modelo biomecánico para calcular las magnitudes angulares de relevancia clínica sobre la base de cada orientación. Para el cálculo de los ángulos de articulación, se definió un sistema de referencia local para cada segmento.

El protocolo de evaluación cinemática consistió en la realización de una sesión utilizando el Sistema VR Toyra ®, concretamente la Sesión de Evaluación. Se analizaron los rangos de movimiento de los hombros, codo y muñeca con la herramienta MATLAB® (Matrix House, Cambridge, UK), obteniendo así 14 variables cinemáticas diferentes: abducción paso a paso del hombro (AbdshoulderS), Abducción completa del hombro (AbdshoulderC), flexión del hombro (FlexshoulderS), flexión completa del hombro (FlexshoulderC), rotación del hombro (Rotshoulder), flexión del codo paso a paso (FlexelbowS) paso, flexión completa del codo (FlexelbowC), extensión del codo (Extelbow), supinación del codo (Supelbow), pronación del codo (Proelbow), extensión de la muñeca (Extwrist), flexión de la muñeca (Flexwrist), desviación radial de la muñeca (Raddevwrist) y desviación cubital de la muñeca (Uldevwrist).

Finalmente, se han definido cinco métricas diferentes, basadas en los datos cinemáticos obtenidos durante las sesiones Toyra ®. La amplitud de la articulación y la amplitud de alcance reflejan magnitudes que se usan comúnmente en las evaluaciones clínicas, pero las novedades en este estudio son que pueden ser calculadas mientras se realizan AVDs y se comparan con un patrón de referencia saludable. Esto es de especial interés en el campo de la rehabilitación ya que estaremos expresando rangos de movimiento plenamente funcionales, traducidos directamente a tareas reales. Las otras 3 métricas, agilidad, exactitud y repetibilidad presentan nuevas definiciones de conceptos que no son fácilmente medibles por métodos convencionales.

Participaron en el estudio quince sujetos (11 varones y 4 mujeres con lesión completa de la médula espinal, edad media 35,33 ± 14,4 años, 4,8 ± 2,37 meses desde la lesión).

3.2 Estudio BMI + Realidad Virtual + FES (capítulo 3)

Hemos diseñado un sistema de neurorrehabilitación, que incluye un BMI que decodifica la intención del paciente en tiempo real y activa los otros 2 subsistemas simultáneamente: FES y realimentación virtual. La retroalimentación virtual se visualizó en la pantalla al mismo tiempo que se generaba el agarre. Consistió en una mano abierta virtual que se cerraba al detectarse la intención motora del paciente. El sistema diseñado en este trabajo consistió en los siguientes subsistemas:

1) Interfaz cerebro-máquina.

2) Estimulador eléctrico funcional (FES).

3) Retroalimentación de la realidad virtual e interfaz gráfica de usuario.

4) Controlador de alto nivel (HLC).

Se realizó un estudio de viabilidad con 4 pacientes con SCI (ASIA B, C o D), quienes realizaron 5 sesiones con el dispositivo BMI + FES + realidad virtual. El objetivo fue analizar la viabilidad y usabilidad del dispositivo como herramienta para la neurorrehabilitación y evaluar los efectos inmediatos sobre los pacientes después de usar el sistema. Para ello se aplicó la intervención a uno de los brazos del paciente, de ahora en adelante denominado "brazo estimulado", mientras que el otro se denominará "brazo no estimulado".

Los pacientes usaron su intención de movimiento para desencadenar un movimiento de agarre con FES, mientras que simultáneamente recibían una retroalimentación visual de un cierre virtual de la mano. Se realizaron evaluaciones clínicas iniciales y finales, así como una prueba de usabilidad y una prueba de esfuerzo que los 4 pacientes respondieron después del estudio. El protocolo experimental consistió en 5 sesiones, con una duración aproximada de una hora cada una.

3.3 Métricas de neuroplasticidad (capítulo 4)

Se han aplicado dos métricas de FC a los datos de EEG para analizar su desempeño en un contexto de BMI: parte imaginaria de coherencia (IC) y versión ponderada del índice de retardo de fase (WPLI). Ambos son menos sensibles a la conducción de volumen que las otras métricas, por lo tanto creemos que podrían ser adecuados en un entorno de BMI. IC es una métrica lineal, mientras que WPLI no es lineal, por lo tanto, la comparación de las interacciones cerebrales que ambas métricas son capaces de revelar, nos permitirá determinar si la linealidad del EEG puede ser asumida o no. Después de estudiar qué interacciones cerebrales están más directamente relacionadas con el estado clínico de los pacientes, desarrollaremos una nueva métrica que incluya esta información, para ofrecer una métrica de sincronía global (GSYM) que podría usarse como un método de evaluación de los cambios cerebrales durante las terapias de neurorrehabilitación. Esta métrica pretende ofrecer una síntesis de los cambios en la actividad cerebral de diferentes áreas.

Las grabaciones EEG utilizadas para calcular las métricas de neuroplasticidad provienen de los experimentos BMI + FES + realidad virtual ya descritos en el Capítulo 3. En ellos, 4 sujetos realizaron 5 sesiones controlando un FES y una retroalimentación virtual directamente desde su propia intención, mediante MA de la parte superior. Hubo sesiones de entrenamiento (utilizadas para recopilar datos para entrenar al clasificador) y sesiones interactivas (con retroalimentación FES y realidad virtual). Se analizaron las grabaciones de EEG de las sesiones de entrenamiento después de la aparición de la señal (por lo tanto, desde t = 0 s a t = 3 s), porque estamos interesados en estudiar la actividad cerebral relacionada con la intención motora. Con el fin de encontrar correlaciones entre las evaluaciones clínicas y métricas de neuroplasticidad, se consideró la primera y la última sesión de cada paciente.

Después de calcular GSYM a partir de señales EEG de los experimentos BMI + FES + realidad virtual, queríamos validar esta métrica en un conjunto de datos diferente, con el fin de estudiar su aplicabilidad en diferentes experimentos de BMI. Para este objetivo, hemos calculado GSYM también en un conjunto de señales de EEG de experimentos en los que 4 pacientes con SCI controlaron un exoesqueleto de miembros inferiores mediante un BMI.

4. Conclusiones

A continuación enumeramos las conclusiones obtenidas en cada capítulo:

Capítulo 2

- Se ha diseñado un nuevo conjunto de métricas cinemáticas para evaluar la función de los miembros superiores por medio de un sistema de rehabilitación de la realidad virtual.
- Las características clave clínicas se han traducido en formulaciones matemáticas que comprenden los datos cinemáticos registrados por los sensores inerciales.
- Se ha demostrado que algunas de las métricas cinemáticas definidas están correlacionadas con las escalas clínicas estándar, lo que demuestra su significado clínico.
- El conjunto de métricas cinemáticas proporciona información objetiva de relevancia clínica que permite la segmentación del paciente, así como una evaluación más precisa, que es esencial para facilitar el uso de tecnologías de rehabilitación en entornos clínicos.
- Estas métricas, junto con el sistema de realidad virtual, ofrecen la posibilidad de realizar evaluación y terapia simultáneamente, lo cual es muy importante para refinar el tratamiento del paciente.

- Se ha definido un método para minimizar la influencia de movimientos involuntarios en la evaluación de la agilidad considerando la relación entre la media y la máxima velocidad angular.
- En comparación con trabajos anteriores, este es uno de los primeros estudios que han encontrado información clínicamente relevante en un entorno virtual de rehabilitación, recogiendo parámetros de un conjunto complejo y variado de ejercicios realizados por pacientes con SCI.

Capítulo 3

- La novedad de la integración de BMI, FES y la realidad virtual como terapia para los pacientes con lesión medular, permitiendo a los pacientes controlar ambos sistemas por sí mismos, sin ayuda externa
- El sistema mostró altos niveles de precisión a lo largo de las diferentes sesiones (79,13% en promedio).
- La precisión del sistema en la detección de la intención de movimiento permaneció estable durante las diferentes sesiones, por lo que podemos concluir que los algoritmos diseñados son suficientemente robustos.
- El análisis discriminante escaso, una técnica de aprendizaje automático para reducir la dimensionalidad y clasificar los datos, se ha aplicado con éxito al dominio BMI.
- Un algoritmo que combina características temporales (MRCP) y características de frecuencia (ERD) ha demostrado ser eficaz para los pacientes con SCI para detectar intento de movimiento de los miembros superiores.
- Los algoritmos desarrollados en este trabajo también permiten analizar las características neurofisiológicas más relevantes para cada paciente, lo cual es muy importante para proporcionar un sistema que pueda servir para realizar la terapia y también para evaluar a los pacientes.
- El retardo entre la intención de movimiento y la respuesta lograda por el sistema es suficientemente corto para proporcionar a los pacientes la sensación de control inmediato de FES y VR, que es esencial para el éxito de la terapia.

- El dispositivo de terapia ha sido probado con seguridad por los pacientes, sin observar efectos adversos en ninguno de ellos.
- En términos de usabilidad y esfuerzo, todos los pacientes mostraron su satisfacción después del uso de la aplicación.
- Prometedores resultados clínicos han sido obtenidos por 4 pacientes con SCI después de realizar 5 sesiones de terapia con el sistema, como pequeñas mejoras de su agarre cuantitativo en el brazo estimulado en comparación con el brazo no estimulado. Por lo tanto, concluimos que el diseño del sistema cumplió correctamente los objetivos deseados.
- Los resultados de este trabajo apoyan la factibilidad de una realimentación de la realidad virtual BMI + FES + para ser considerada como una herramienta terapéutica para la rehabilitación de los miembros superiores.

Capítulo 4

- La novedad de la aplicación de las métricas de FC en el contexto de los experimentos basados en BMI con pacientes con lesión medular.
- El diseño de una métrica global de sincronía (GSYM) que comprende las interacciones entre áreas cerebrales más estrechamente relacionadas con el estado clínico de los pacientes.
- La definición de una metodología para extraer información clínicamente relevante de señales de EEG que podrían aplicarse en diferentes escenarios, como los experimentos BMI + FES + realidad virtual y BMI + Exoesqueleto descritos en este estudio.
- Mediciones lineales de FC, como IC, y no lineal, como WPLI, revelan similares interacciones cerebrales en el contexto de un estudio de BMI.
- La parte imaginaria del espectro es una forma fiable de determinar las interacciones neuronales incluso en presencia de ruido.
- Los sistemas basados en EEG de superficie, a pesar de su baja resolución espacial, junto con algoritmos robustos para la minería de datos, ofrecen una interesante herramienta para evaluar la neuroplasticidad, especialmente útil para

desarrollar sistemas de neurorrehabilitación, debido a su portabilidad y no invasividad

- Existen correlaciones significativas entre los cambios en la interacción cerebral y el estado físico de los pacientes con SCI, antes y después de las terapias basadas en el BMI: BMI + FES + realidad virtual y BMI + Exoesqueleto.

CHAPTER 1: INTRODUCTION

This thesis is focused on the innovative use of Brain-Machine Interfaces and Virtual Reality to evaluate and rehabilitate patients with Spinal Cord Injury (SCI). In the first part of the thesis (chapter 2), a virtual reality system was designed with exercises performed using inertial sensors and a new set of metrics from the inertial recordings was defined with the aim of evaluating patients' status, showing correlations with clinical scales. In the second part of the thesis (chapter 3), virtual reality is directly controlled with the patients' electroencephalographic signals, by means of a Brain-Machine Interface in combination with a Functional Electrical Stimulator, with the aim of promoting recovery of grasping movement. In the third part of the thesis (chapter 4), a Brain-Machine Interface is used with the objective of evaluating neural interactions through a methodology that makes use of imaginary coherence between different areas of the brain, combined with graph theory metrics. The defined metrics showed correlations with clinical scales in two different kinds of Brain-Machine Interfaces with different patients.

In order to introduce the need of developing new technologies for SCI patients, I would like to emphasize that SCI dramatically changes the lives of those that suffer it. It is in most of cases accompanied by a severe disability of upper and lower limbs, depending on the level of injury. During the last decades, there have been plenty of studies approaching the challenge of regenerate or replace the damaged areas of the spinal cord. In the meanwhile, technologies have been rapidly improving in several fields such as virtual reality, robotics, mobile applications, wearable devices and machine learning. The progressive introduction of these technologies in the medical field has allowed the definition of new paradigms of treatment for SCI patients. One of these new paradigms includes the use of virtual reality (VR) to promote rehabilitation.

VR allows the immersion of the patients in a new rehabilitation environment, where they are able to interact with both virtual and real elements while performing exercises and tasks specifically designed to improve their abilities. Moreover, at the same time that they are performing the tasks, motion capture sensors (mocaps) can be used to monitor their progress, offering a powerful tool to the clinicians in order to adjust treatments and to accurately detect changes in the patients' functionality. Therefore, one of the main advantages of the use of VR games for rehabilitation is that they allow simultaneous exercise and assessment, by means of mocaps.

Although several previous studies have focused on developing metrics to assess disability with mocaps, there are few examples that have shown the clinical relevance of those metrics. One of the main difficulties is that some of the aspects that determine the physical status of the patients have not been yet objectively defined. Therefore, it is essential to establish appropriate definitions of the rehabilitation essential concepts, such as agility, repeatability or precision, and then to translate these concepts into mathematical definitions that can be computed from the wearable sensor recordings.

In the first part of this thesis, we describe the definition and the application of a set of metrics to evaluate the functional status of patients with SCI in the context of a VR system for upper limb rehabilitation. The aim of this first study is to demonstrate that VR can be used, in combination with mocaps, to rehabilitate and evaluate simultaneously. 15 SCI patients carried out 3 sessions with Toyra VR System and the defined set of metrics was applied to the recordings obtained with the inertial sensors. There were correlations between some of the defined metrics and some of the clinical scales frequently used in the rehabilitation context.

Rehabilitation with Toyra focused on patients with a certain degree of mobility in the upper limbs. However, VR use for rehabilitation is not limited to this kind of patients. There also exists the possibility of exerting rehabilitation even in the most severe cases. The field of Brain-Machine Interfaces (BMI) opened the door to a new paradigm of rehabilitation, in which the movements are commanded from the patient's own intention, throughout his/her electroencephalographic (EEG) signals. This allows the introduction of VR in the rehabilitation of patients that are not able to move their limbs. In the second part of the thesis, we have combined a VR feedback with a Functional Electrical Stimulator (FES), both of them controlled by a BMI, to develop a new kind of therapeutic approach for patients. The system has been used by 4 SCI patients that attempted to move their hands. This intention triggered simultaneously the FES and the VR feedback, closing patients' hand and showing them an additional source of feedback to complement the therapy. VR might serve to overcome one of the limitations of FES, which is that patient's hand does not always react to the electrical current in the same way, and, therefore, sometimes the hand closes with different patterns. By displaying the VR hand that always closes correctly, we can always provide the patient with a positive feedback, independently from the response of his/her limb to the electrical stimulation. Moreover, VR could offer an additional reward to the therapy, by supplying virtual objects in order to perform goal-directed tasks.

This work is to the best of our knowledge, the first that integrates BMI, FES and virtual reality as therapy for SCI patients. Promising clinical outcomes were obtained by 4 patients with SCI after performing 5 therapy sessions with the system, showing good levels of accuracy throughout the different sessions (79.13 % on average). Moreover, an automatic procedure for feature extraction based on SDA was developed in order to identify the EEG channels that most faithfully reflect the underlying neurophysiological phenomena (MRCP and ERD) in SCI patients. Three different subsystems (BMI, FES and virtual reality) were successfully integrated by means of a HLC controller, giving rise to a system that works transparently to the user, allowing the patients to control the FES and virtual reality by themselves, without external assistance.

Both systems (Toyra and BMI+FES+VR) already described in the first two parts of the thesis have been designed with the purpose of promoting neuroplasticity, that could be defined as the process that undergoes the nervous central system to restore and repair the areas that have been damaged by an injury, such as Spinal Cord Injury. In order to evaluate the efficacy of new technologies for neurorrehabilitation, the most common approach is usually to measure the effects in the physical status of the patients, as we have done in the first part of the thesis with the defined kinematic metrics. However, neurological recovery usually precedes functional recovery. Therefore, it is also important to study the changes in the neuronal activity of patients after performing a therapy.

There are many different techniques to measure brain interactions, many of them are based on fMRI signals. On the other hand, EEG offers an interesting alternative for the development of neurorrehabilitation technologies, since it is portable and cheaper than fMRI. Besides, it has a better time-resolution, so it allows to study in a precise way the temporal interactions between different areas of the brain. In the third part of the thesis we have defined a new metric to study brain connectivity changes in SCI patients, that comprises physiological information with phase-signals from the brain and network theory parameters. The aim of this study has been to extract clinically relevant information from EEG activity when performing BMI-based therapies (with FES+VR in one study and with exoskeleton in another one). The aim was to develop new approaches to measure if new neurorrehabilitation technologies (BMI, VR, exoskeletons) have effectively promoted neuroplasticity.

CHAPTER 2: KINEMATIC METRICS BASED ON VIRTUAL REALITY AS AN ASSESSMENT OF THE UPPER LIMB REHABILITATION IN PEOPLE WITH SPINAL CORD INJURY

1. INTRODUCTION

It has been estimated that the prevalence of spinal cord injury (SCI) is 223-755 per million inhabitants, with an incidence of 10.4-83 per million inhabitants per year [39]. Fifty per cent of the patients with SCI are diagnosed as complete, and in one-third of the patients, the SCI is reported as tetraplegic.

In patients with tetraplegia, the arm and hand function is affected to a different degree, depending on the level and severity of the injury [40].

Several studies have shown that the improvement in upper extremity function is one of the greatest needs in patients with tetraplegia [41]. In this respect, upper extremities therapy in people with tetraplegia plays a key role during the rehabilitation.

Virtual Reality (VR) has emerged in the rehabilitation context in an effort to promote task oriented and repetitive movement training of motor skills while using a variety of stimulating environments [42]. This approach can increase patient motivation, while extracting objective and accurate information enables the patient's progress monitorization.

The aim of VR is to create a feeling of immersion within the simulated environment so that the patient's behaviour during the game resembles as much as possible his/her behaviour in the real world.

There are different motion capture technologies that permit to transfer the actual patient's movement to a virtual environment. One of them is the inertial measurement technology. There are several advantages of using Inertial Measurement Systems (IMUs) as motion capture systems for VR applications, since they are compact, light, resistant to environmental interference and easy to wear.

VR technology increases the range of possible tasks, partly automating and quantifying therapy procedures, and improving patient motivation using real-time task evaluation and reward [43]. It also permits the standardization of tasks and the recording of kinematic data during the execution of these tasks, making it an interesting tool for assessment of the rehabilitation progress.

Evaluation of the SCI patient's functional status is usually carried out by means of clinical scales, although they have a high subjective component depending on the observer who scores the test. Therefore, a better understanding of human movement requires more objective testing and accurate analysis of motion to describe the arm movements more precisely and specifically during functional testing. Kinematic analysis is one such method [44].

Clinical scales are not very sensitive to slight improvements in functionality, neither they are able to establish the biomechanical characteristics that explain the clinical changes in the scores obtained by the patients during their rehabilitation. Thus, it is important to find the kinematic parameters that correlate with clinical scales. In a previous study from our group, correlations were already found between kinematic data and clinical scales [45]. These scales inform about global disability. But they include specific items related to upper limb impairment. Therefore, it seems relevant to go deeper in the analysis trying to obtain a more specific correlation between kinematics and functionality.

It is important to underline that kinematic data by themselves are not always sufficiently clear and understandable for clinicians in order to reliably evaluate a patient. However, combining them to obtain new metrics could enhance their potentiality as tools for physical assessment.

The objectives of the present study are: (i) to analyze the correlations between kinematic data after performing upper limb tasks included in the VR System Toyra, considering patients with tetraplegia and clinical sub-scales more closely related to upper limb function (ii) to define kinematic metrics based on data recorded by the VR System Toyra ® that could offer additional information to clinicians and (iii) to analyze the correlation between the defined kinematic metrics and clinical scales, by applying them to a group of 15 patients with tetraplegia.

2. STATE OF THE ART

2.1. KINEMATIC METRICS

Quantification of upper extremity movements has been researched for many years. One of the first studies in this field was carried out by Fitts in 1954, with the aim of analyzing the speed-accuracy trade-off and, as a result, calculating the performance and an index of difficulty of a task from three parameters: the time spent on performing the movement, the distance and the size of the object to be reached [1].

The interest in obtaining parameters that could provide relevant information to clinicians from the quantification of the upper extremity movements is relatively recent. To this aim, there are some studies that analyze the movements performed by patients with neurological disorders during reaching tasks and also while drawing [2]–[4]. There are also studies in which a basic activity of daily living (ADL) has been analyzed, such as the drinking task, in people with stroke [5] or SCI [6], and also some metrics have been developed for a specific task [7], [8].

Some of the kinematic parameters calculated to obtain information that could be clinically relevant are the time spent on the task, maximum [46] and mean velocity [2], range of motion during the movement [6], [44], [47]; the inter-joint correlation between the shoulder and elbow flexion movements [4]–[6]; and the number of peaks in the speed profile [5].

In neurological rehabilitation, the assessment of upper limb motor recovery should include smoothness, efficacy and efficiency of the movement [3]. In this study, metrics related to these movement characteristics have been proposed:

- Efficacy: the percentage of the task successfully completed by patient's voluntary movement.
- Accuracy: the spatial deviation between the path followed by the patient's hand and the theoretical trajectory (in other studies it has been named "trajectory error").
- Efficiency: it is a measure of the ratio between the length of the hand trajectory during the movement and the length of the theoretical trajectory.

- Smoothness: it is computed from the speed profile of the hand during the movement as the number of peaks.

These metrics are more easily applicable to reaching movements, in which the theoretical hand trajectory is the straight line between the starting point and the target location. Other authors have calculated the trajectory curvature from the first and second derivatives of position with respect to the time [48]. There also examples of combination of time and distance measurements, together with the size of an object to reach, in order to provide a metric of the difficulty of task [49].

Most of the proposed metrics are a measure of the error or deviation between two variables. So, for example, smoothness as the number of peaks is a measure of error, since a higher number of peaks is related to a less smooth movement. The same occurs in accuracy and efficiency metrics, in which a decrease in these metrics indicates an improvement in motor performance for a functional task. For that reason, it seems necessary to obtain parameters that could be directly proportional to the patient's functional status [50].

Other authors have quantified accuracy as a spatial overshoot, considered as the excess of distance with respect to the target during reaching tasks [51]. There are also some metrics that quantify smoothness from changes in acceleration, by calculating the number of zero-crossings [52].

In most of the aforementioned studies, photogrammetry systems have been used to record the motion information, which are the gold standard for biomechanical analysis, due to their accuracy. In contrast, in this work, we extracted information from inertial sensors, because they allow designing systems to be used out of the environment of a motion analysis laboratory, since they do not require additional cameras to capture movements. This is of special interest for the development of virtual reality systems for rehabilitation. Moreover, many of the previous studies focused on a specific task, but we are rather interested in metrics that could comprise many different movements in a single value, to offer a global measurement that could be related with functionality. There is still a need of further research about the validity of this kind of metrics in a clinical environment [9], hence we believe that it is necessary to look for relationships between clinical parameters and kinematic metrics.

2.2. CLINICAL SCALES

There are plenty of scales in the literature which attempt to assess the patients in order to detect functional changes during the upper limb rehabilitation process [53]. These assessment scales include grasping, holding, and manipulating objects, which require the recruitment and complex integration of muscle activity from shoulder to fingers.

The upper extremity motor function tests are classified in the following categories: (1) Strength tests; (2) Functional tests; (3) ADL tests [54]. In this section, only the clinical scales that were used in this study and those that will be mentioned in the "Discussion" section are described.

Strength tests:

The evaluation of key muscle groups is essential to identify the motor level in patients with tetraplegia. Muscular strength offers an important indicator of patients' progress and it is regularly used to perform neurological classification of SCI patients, to plan the therapy and to evaluate the outcome of a determined intervention [55].

- Motricity Index: itassesses power and range of active movement for shoulder abduction, elbow flexion, and pinch between the thumb and index finger. The total score is rated between 0 (no movement) and 100 (normal movement). The total score of the scale has been evaluated and also each of the sub-scores: shoulder abduction (UL MIAbdShoulder), elbow flexion (UL MIFlexelbow) and pinch (UL MIPinch). [56].

Functional tests:

Functional tests are designed to evaluate the abilities of the patients by performing a determined series of tasks, standardized to allow comparison between subjects and populations. Those tasks have been specifically designed to quantify several aspects of upper limb function, such as dexterity, precision, speed, bilateral movements or fine hand function. Some functional tests are designed for a specific population, while others have a general purpose:

- Jebsen Taylor Test of Hand Function [57] is a scale to assess the hand disability and the improvements in the hand functionality gained by therapeutic procedures in patients with hand disabilities[54], but, due to the kind of activities proposed in the test, it is necessary to have a minimum of hand and fingers' dexterity to complete it. It has been used for different pathologies, such as cerebral palsy, SCI or arthritis and it consists of 11 tasks such as writing, turning over cards, picking up different objects, etc. The outcome measure is the time taken to complete the tasks.
- The Action Research Arm test (ARAT) provides a rapid yet reliable and standardized performance test appropriate for use in assessing recovery of upper limb, but it is used solely in stroke patients[58]. It consists of 19 sub-items that comprise 4 sub-tests: grasp, grip, pinch and gross arm function. Each item is rated in a 4-point ordinal scale from 0 to 3.
- The Fugl-Meyer Assessment (FMA) was developed to measure sensorimotor stroke recovery based on Twitchell and Brunnstrom's concept of sequential stages of motor recovery in patients with hemiplegic stroke [59]. It is a general scale, not focused only in upper limb assessment, but also comprising areas such as balance, sensory function and pain.
- Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): this scale has been specifically designed to assess upper limb impairment in patients with SCI [60]. It evaluates sensitivity, prehension and strength with 6 different subtests.

ADL tests:

This kind of scales is especifically focused in the quantification of ADL performance. Therefore, they may require the patient either to carry out those activities or to answer a questionnaire rating his/her performance. Two of the most used ADL evaluations for patients with tetraplegia are the Functional Independence Measure (FIM) and the Spinal Cord Independence Measure II (SCIM II). These tests are validated and reliable, and show strong correlation with each other [46].

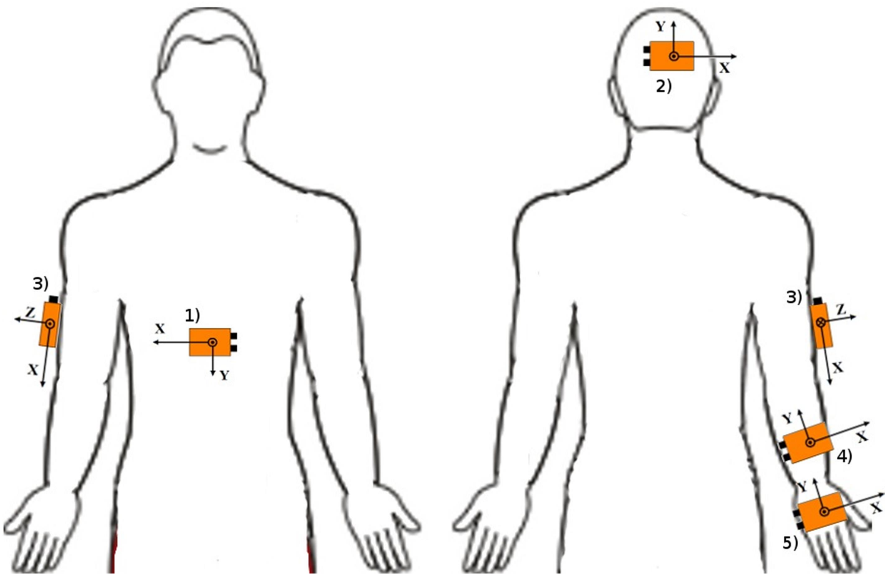
- The Motor Activity Log (MAL) is a scripted, structured interview that was developed by Taub *et al*. to measure the effects of Constraint-Induced Movement (CI) therapy on use of the more-impaired arm outside the laboratory in individuals with stroke [61]. It evaluates the quality and amount of movement during several daily tasks. Each item is rated between 0 and 5.
- Functional Independence Measure (FIM): The purpose of this scale is the measurement of the severity of the patient's disability and the outcomes of medical rehabilitation in patients. The FIM has a good clinical inter-rater agreement in patients undergoing inpatient medical rehabilitation (ICC=0.97). FIM scores were significantly lower in complete C4 tetraplegics than in C6 tetraplegics, which indicated that the FIM is sensitive enough to differentiate between different levels of injury [54].
- Spinal Cord Independence Measure II (SCIM II): it was specifically developed for SCI persons, in order to make the functional assessments of persons with paraplegia or tetraplegia more sensitive to changes. The SCIM has a good inter-rater reliability (r=0.98). Besides, the sensitivity of the SCIM is higher than the sensitivity of the FIM, showing in patients with tetraplegia that this scale missed 22% of the functional changes detected by the SCIM [54]

Regarding the kind of patients of this study, with a complete SCI at levels between C5 and C8, Motricity Index, FIM and SCIM tests are considered the most suitable ones and, therefore, they have been chosen for this study.

3. METHODS

3.1 CAPTURED RAW KINEMATIC DATA

For the kinematic capture process, a motion capture system based on inertial sensors MTx Xsens Company (Xsens Inc, Netherlands) has been used. In this application, 5 inertial sensors were located on the head, trunk, arm, forearm and hand. The placement of the sensors can be seen in Figure 2.1. The sensors capture the main upper limb movements: shoulder flexion/extension, shoulder abduction/adduction, shoulder rotation, elbow flexion/extension, pronosupination, wrist flexion/extension and wrist ulnar/radial deviation. These movements are translated in real-time to an avatar that appears on the screen in a virtual environment called Toyra, specifically designed to perform upper limb rehabilitation tasks. This system comprises two kinds of sessions:



a b

Fig 2.1 Placement of the inertial sensors: a, frontal view; b, posterior view. The sensors were located on the trunk (1), the back of the head (2), the right arm (3), the forearm (4) and the hand (5).[62]

- Evaluation sessions: designed to measure ranges or motions for the aforementioned upper limb movements. During them, patients are required to reach their maximum amplitudes, by touching spheres that appear sequentially on the screen.
- Activities of daily living (ADL) sessions: they were designed to simulate ADLs such as eating with a spoon, washing with a sponge or grasping different objects.

The avatar and the virtual environment can be seen in Figure 2.2.

Fig 2.2 Avatar and virtual environment during a Toyra session

A biomechanical model, previously reported [62], was developed, based on inertial sensor data and Upper Limb (UL) anthropometric data. The MTx inertial sensors include tri-axis accelerometers, gyroscopes and magnetometers. As long as the inertial sensors only provide information of the orientation of each body segment, a biomechanical model is required to calculate the angular magnitudes of clinical relevance on the basis of each orientation. The kinematic chain proposed in this model consists of 7 DoF (Degrees of Freedom): three in the shoulder joint (flexion-extension, abduction-adduction and external-internal rotation); two in the elbow joint (flexion-extension and pronation-supination) and two in the wrist (palmar-dorsal flexion and radial-ulnar deviation). In the trunk, the inertial sensor was placed over a rigid support, parallel to the spine. The trunk reference system is defined with vector X parallel to the line from right to left acromion, and vector Z parallel to the longitudinal axis of the trunk.

For the computation of the joint angles, a local reference system was defined for each segment. Therefore, it was necessary to transform the orientation matrix from the global to the local reference system, by means of rotation matrices (${}^{G}R_{S}$) between both systems, that contain the three vectors representing the sensor reference system with respect to Earth's magnetic and gravity vectors as follows:

$$^{G}R_S = [\overrightarrow{X_S} \quad \overrightarrow{Y_S} \quad \overrightarrow{Z_S}] = \begin{bmatrix} X_x & Y_x & Z_x \\ X_y & Y_y & Z_y \\ X_z & Y_z & Z_z \end{bmatrix}$$

The kinematic assessing protocol consists in the execution of one test using the VR System Toyra ®, the Evaluation Session, whose principal objective is to assess the patient's functional capacity, based on the record of the kinematic variables during the execution of analytical movements of the UL joints, in each degree of freedom. The same therapist carried out the Evaluation Sessions to all patients, in order to minimize the errors due to the different placement of the sensors by different therapists. In Figure 2.3, the position of a patient in front of the screen during the execution of a session with Toyra ® can be seen.

Joint ranges of motion (ROM) of shoulder, elbow and wrist were analysed with the mathematics software tool MATLAB® (Matrix House, Cambridge, UK), thus obtaining 14 different kinematic variables: step-by-step shoulder abduction (AbdshoulderS), complete shoulder abduction (AbdshoulderC), step-by-step shoulder flexion (FlexshoulderS), complete shoulder flexion (FlexshoulderC), shoulder rotation (Rotshoulder), step-by-step elbow flexion (FlexelbowS), complete elbow flexion (FlexelbowC), elbow extension (Extelbow), elbow supination (Supelbow), elbow pronation (Proelbow), wrist extension (Extwrist), wrist flexion (Flexwrist), wrist radial deviation (Raddevwrist) and wrist ulnar deviation (Uldevwrist). The "step-by-step" variables have been measured during exercises in which the goals the patients have to reach appear on the screen sequentially from the bottom to the top of the screen, in such a way that they have to perform discrete movements and stay in the object for one second, approximately, needing a minimum of control in the muscles involved in this movement.For the "complete" variables, all goals are displayed at the same time, so that the patients perform a continuous trajectory. The reason to measure

Fig 2.3 Patient performing a Toyra® session

these two kinds of variables separately is that "step-by-step" movements require holding the arm in a fixed position, so the patient needs to exert the task with greater movement control. Depending on the level of SCI, some patients may be able to perform complete movements but not the step-by-step ones.

The Ranges of Motion (ROM) have been calculated from the 14 kinematic variables previously mentioned, as the difference between the maximum and the minimum value reached by the patients during each specific exercise.

3.2 KINEMATIC METRICS

With the aim of evaluating the functional capacities of SCI patients during the realization of the therapy with Toyra, a novel set of kinematic metrics have been defined. We have previously specified a list of requirements that all of the metrics have to fulfil:

1) They have to be computed from kinematic information recorded: trajectories and velocities of the 3 upper limb joints (wrist, elbow and shoulder).
2) They have to allow comparisons with a healthy reference pattern, getting a percentage of patient's performance against that healthy reference.

3) They have to be flexible, in order to allow its application to different exercises of a virtual reality rehabilitation system.

4) They have to reflect clinically relevant features.

Finally, five different metrics have been defined, based on the kinematic data obtained during the Toyra ® sessions. *Joint amplitude* and *reaching amplitude* reflect magnitudes that are commonly used in clinical assessments, but the novelties in this study are that they can be calculated while performing ADLs and they are compared with a healthy reference pattern. This is of special interest in the rehabilitation field since we will be expressing fully functional ranges of motion, directly translated into real tasks. The other 3 metrics, *agility*, *accuracy* and *repeatability* present new definitions of concepts that are not easily measurable by conventional methods:

-*Joint Amplitude*: it has been defined as the sum of the ROMs obtained by a patient, normalized by the corresponding ROM obtained by a healthy subject, defined as "ideal ROM":

$$JA = \frac{\sum_{i=1}^{i=14} k_i \cdot ROM_i}{\sum_{i=1}^{i=14} k_i \cdot idealROM_i} \cdot 100[\%]$$

Where:

ROM_i[º]= degrees covered by the joint under study (it is important to remark that each session exercise has been designed to check the performance of a single joint. For example, the shoulder abduction exercise will measure the shoulder ability, despite some other joints are, to a lesser extent, also involved in this movement)

k_i= weighting coefficients of the exercises, chosen to emphasize the ROMs that are more related to the motor abilities of the patient.

-*Reaching Amplitude*: it has been defined as the range that the patient is able to reach for the three different axes (X,Y,Z). The X-axis has been established horizontally, parallel to the screen, the Y-axis horizontally perpendicular to the screen, and the Z-axis is vertical, parallel to the screen.

It is expected that, as a patient with SCI is able to move closer to the objects that surround him, he would get more autonomy and functionality.

Reaching Amplitude is calculated for each axis as the difference between the maximum and the minimum value of the patient's hand position, getting a range of reaching for each exercise, while the patient is carrying out the three-dimensional movements required by the task. Then, these ranges of reaching are summed up and normalized by the sum of ranges obtained by a healthy subject. The final result is calculated as a weighted sum of these factors for each of the 3 axes.

$$RA = \sum_{j=1}^{j=3} k_j \cdot \frac{\sum_{i=1}^{i=14} \max(h_{j_i}) - \min(h_{j_i})}{\sum_{i=1}^{i=14} \max(idealh_{j_i}) - \min(idealh_{j_i})} \cdot 100[\%]$$

Where:

k_j=weighting coefficient, to assign each axis a different influence in the total reaching amplitude.

h_{ji}= hand's trajectory for each axis *j,* for each exercise *i* carried out by the patient.

$idealh_{ji}$= hand's trajectory for each axis *j,* for each exercise *i* carried out by a healthy subject.

Depending on the value assigned to k_j (being j=1 the X-axis, j=2 the Y-axis and j=3 the Z-axis), it is possible to compute the *reaching amplitude* separately for each direction. For the total reaching amplitude, the same weight $k_j = 1$ will be assigned to the 3 axes.

-*Accuracy*: it has been calculated considering 2 parameters: mean distance from the trajectory performed by the patient's hand to the ideal hand trajectory performed by a healthy subject (d_{mean}), and the maximum distance between these 2 trajectories (d_{max}).

$$Ac = 100 - \sum_{i=1}^{i=14} 2 \cdot d_{mean_i} \cdot \left(1 + \frac{d_{mean_i}}{d_{\max_i}} \right)$$

The idea of this formula is to penalize the accuracy of those trajectories that present several peaks of deviation with regard to the ideal trajectory. If they have few peaks, d_{mean} will not be affected to a great extent by these peaks, so that $d_{mean} << d_{max}$ and, thus, the penalization for the accuracy would be approximately $2d_{mean}$.

However, if the number of peaks of deviation is higher, d_{mean} will be affected by these values, and d_{mean} will increase. Considering an extreme case, in which there were so many peaks of deviation that $d_{mean} \approx d_{max}$, then the penalization for the accuracy would be $4d_{mean}$, much higher than in the previous case.

In order to obtain values in percentages, as in previous metrics, accuracy has been normalized by the accuracy value obtained by a healthy subject:

$$Ac_{norm} = \frac{Ac}{Ac_{ideal}} \cdot 100[\%]$$

-*Agility*: it has been considered that an agile movement should be not only fast but also precise. To this aim, this metric takes into consideration three parameters: accuracy (as defined previously), angular velocity and time needed to execute the task.

$$Ag = 100 - \sum_{i=1}^{i=14} \frac{20 \cdot \frac{d_{mean_i}}{d_{\max_i}} + 30 \cdot \frac{v_{\max_i}}{v_{mean_i}} + 50 \cdot \frac{t_i}{t_{ideal_i}}}{100}$$

Where:

d_{meani}[m] = mean distance from the trajectory performed by the patient's hand to the ideal trajectory of a healthy subject's hand.

d_{maxi} [m] = maximum distance between the trajectory performed by the patient's hand and the ideal trajectory of a healthy subject's hand.

v_{maxi} [º/s] = maximum angular velocity of the joint under study in each exercise.

v_{meani} [º/s] = mean angular velocity of the joint under study in each exercise.

t_i [s] = time spent by the patient on performing the exercise *i*.

t_{ideal} [s] = time spent by a healthy subject on performing the exercise *i*

The first term of the agility penalization regards the accuracy error, and it has been explained previously.

The second term is regarding angular velocity. A very high maximum angular velocity is penalized, unless the mean velocity is also high. The reason to calculate it in this way is that patients with a badly preserved functionality will carry out the exercises quite slowly, obtaining a low mean angular velocity, but they will also carry out uncontrolled movements, for example dropping the arm, thus getting a high maximum angular velocity. Therefore, it is important to evaluate the relationship between the maximum and the mean angular velocity, not only each of them separately.

The third term takes into account the time spent by the patient on performing the exercise, in relation with the time spent by a healthy subject on performing the same exercise.

In order to express the value as a percentage, as in the previous metrics, agility has been normalized by the agility value obtained by a healthy subject:

$$Ag_{norm} = \frac{Ag}{Ag_{ideal}} \cdot 100[\%]$$

-*Repeatability:* it computes the inverse of the area comprised between the upper and the lower envelope of the repetitions of the same movement during a session:

$$R = k \cdot \sum_{i=1}^{i=8} \frac{k_0}{A_i \cdot \left(1 + \frac{1}{n_{rep}}\right)}$$

Where:

A_i = area comprised between the upper and the lower envelope of the repetitions of the exercise *i*.

k, k_0 = normalizing coefficients used to adjust the scale. Here k=1000 and k_0 have been used.

n_{rep}= number of repetitions for each exercise (it is necessary that all exercises have the same number of repetitions).

For this metric, only the exercises 1 to 8 have been used. They are step-by-step shoulder abduction, complete shoulder abduction, step-by-step shoulder flexion, complete shoulder flexion, step-by-step elbow flexion, complete elbow flexion, elbow extension and shoulder rotation. These exercises are the ones that require the patient to perform a determined trajectory to accomplish the task, so the trajectories of different repetitions should be similar, if the task has been correctly executed. Area A_i has been computed by calculating the upper and the lower envelope along time of all repetitions of the kinematic variable corresponding to exercise *i*. For example, for the first exercise, shoulder abduction curve along time has been used, as can be seen in Figure 2.4 and Figure 2.5.

The area comprised in each exercise is being weighted by the number of repetitions (n_{rep}), because the area tends to increase with the number of repetitions used.

The idea is that, as the patient improves his performance, he should be able to repeat more accurately the same task, decreasing the area between the envelopes.

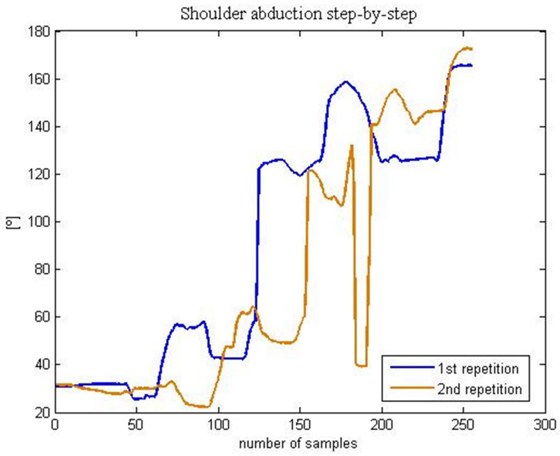


Fig 2.4 Example of the shoulder abduction curves recorded during 2 repetitions of the same movement by a patient.

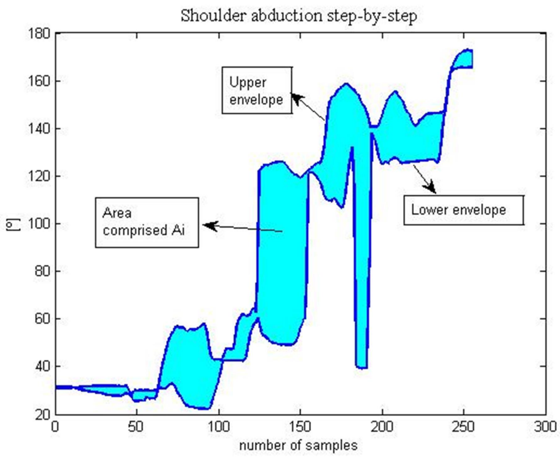


Fig 2.5 Example illustrating the calculation of the *repeatability* for the 2 repetitions shown in Figure 2.4

3.3 PARTICIPANTS

Fifteen subjects (11 males and 4 females with complete spinal cord injury; mean age 35.33 ± 14.4 years, 4.8 ± 2.37 months since injury) participated in the study. Subject's demographic and clinical characteristics are shown in the Table 2.1.

TABLE 2.1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE ANALYSED

<table>
<tr><td>Sex (male)†</td><td colspan="4">11(73.33)</td></tr>
<tr><td>Age [years]*</td><td colspan="4">35.33(14.40)</td></tr>
<tr><td>Time since injury [months]*</td><td colspan="4">4.80(2.37)</td></tr>
<tr><td>Dominance (right)†</td><td colspan="4">9(60)</td></tr>
<tr><td>ASIA (A) †</td><td colspan="4">9(60)</td></tr>
<tr><td>Etiology (trauma)†</td><td colspan="4">14(93.33)</td></tr>
<tr><td rowspan="2">Level of neurological injury (C5-C8)†</td><td>C5</td><td>C6</td><td>C7</td><td>C8</td></tr>
<tr><td>7(46.66)</td><td>4(26.66)</td><td>3(20)</td><td>1(6.66)</td></tr>
</table>

* Continuous variables are expressed as mean and standard deviation values. † Categorical variables are expressed as frequency and percentage of the sample analyzed

Eligible participants met the following criteria: (1) at least 18 years of age; (2) less than 12 months from the injury; (3) motor complete spinal cord injury according to the ASIA´s impairment scale at the level of C5 to C8 (A-B ASIA level [24]); (4) no history of traumatic or cognitive pathology that can affect the Upper Limb (UL) movements; (5) normal or corrected-to-normal vision and hearing; (6) no history of technology addiction; and (7) no history of epilepsy. Each subject gave informed consent voluntarily, which was approved by the local Ethics Committee.

3.4 DATA COLLECTION AND ANALYSIS

Subjects remained seated on their own wheelchair in front of the screen. A total of five MTx IMUs were used to capture movements of the dominant UL, wirelessly connected

(Bluetooth) to a computer via a digital data bus (Master Xbus), which was responsible for the synchronization, data collection and transmission. The IMUs were strategically placed on the trunk, the back of the head, the arm, the forearm and the hand [63]. Each subject received an explanation about how to perform the activity, which consisted of moving the arm trying that the avatar that mimics his or her movements reaches the goals that appear on the screen. Subjects were instructed to perform each of the 14 analytic movements required, including complete and step-by-step shoulder, elbow and wrist motion required. A sampling frequency of 25 Hz was used for the MTx IMUs recordings. The subjects cyclically executed each exercise three times. The mean of these three recordings yielded the final measurement value for each subject.

As described in the "New kinematic metrics" section, some of the metrics require some data recorded from healthy subjects, in order to compare the results of the metrics with a reference value, thus yielding a final value expressed as a percentage with respect to the healthy reference. In order to obtain this reference values, a group of five healthy subjects (2 males and 3 females, with a mean age of 29 years and standard deviation of 6.041) was previously registered. The following parameters were extracted from the healthy subjects and then averaged to obtain the reference values: ROMs, trajectories, time spent on each exercise and absolute value for the metrics.

Neurological examinations of all the patients were performed according to the ASIA standards [24]. The functional examination was done by using three scales. The first scale was SCIM II, which has 16 items divided into three functional areas: self-care, respiration and sphincter management, and mobility. Total score can vary from 0 (minimal) to 100 (maximal) [64]. Only the self-care sub-score has been considered in this study, because it is more closely related with the upper limb function [65]. From now one, this sub-scale will be named Self-care SCIM.

The second assessment scale was the UL part of Motricity Index Scale (UL MI) which assesses power and range of active movement are rated for shoulder abduction, elbow flexion, and pinch between the thumb and index finger. The total score is rated between 0 (no movement) and 100 (normal movement) [56]. The total score of the scale has been evaluated and also each of the sub-scores: shoulder abduction (UL MIAbdShoulder), elbow flexion (UL MIFlexelbow) and pinch (UL MIPinch).

The third scale was Functional Independence Measure (FIM), which consists of 18 items organized in six categories, four corresponding to motor functions (self-care items, sphincter control, mobility items, and locomotion) and two corresponding to cognitive functions (communication and social cognition). The lowest and highest scores of the total ranged from 18 to 126 [66]. As in the SCIM, only the self-care sub-score has been taken into account. From now on, this sub-scale will be named Self-care FIM.
Both the kinematic assessment with Toyra ® and the clinical evaluation were carried out for each patient with a maximum difference of 2 days.

Descriptive analysis including means and standard deviations (SD) for continuous variables was initially performed to characterize each subject and also each group of subjects considering the neurological level of injury (C5-C8). The Pearson correlation coefficient was used to correlate kinematic ROMs with clinical and functional variables. A significance level of p less than 0.05 has been used. All statistical analysis was performed with Matlab (The Mathworks Inc., Natick, MA, USA).

4. RESULTS

Kinematics recorded by Toyra ® (the 14 kinematic variables already mentioned) were obtained for each patient and averaged by levels of neurological injury. These averages can be seen in Tables 2.2, 2.3 and 2.4.
The values obtained by all patients in the clinical scales SCIM, UL MI and FIM have also been obtained and averaged by level of injury, showing the results in the Table 2.5.
Positive strong correlations have been found between kinematic variables and clinical scales in the following parameters: Self-care SCIM and Shoulder Flexion step-by-step ($r=0.776$, $p=0.00067$), Self-care SCIM and Complete Shoulder Flexion ($r=0.74$, $p=0.0016$), UL MI and Shoulder Flexion step-by-step ($r=0.714$, $p=0.0028$) and UL MI and Complete Shoulder Flexion ($r=0.712$, $p=0.0029$).

TABLE 2.2: SHOULDER KINEMATICS PER LEVEL OF INJURY (MEAN ± SD)

	AbdshoulderS	AbdshoulderC	FshoulderS	FshoulderC	Rotshoulder
C5 n=7	73.184± 28.436	72.402± 36.022	103.506± 53.465	107.957± 41.308	114.707± 31.245
C6 n=4	95.903± 34.925	122.465± 26.207	157.989± 28.381	138.222± 56.126	89.824± 22.948
C7 n=3	102.218± 52.31	113.985± 45.117	165.138± 32.002	152.904± 21.112	108.454± 47.901
C8 n=1	137.787±12.10	152.151±13.21	178.582± 12.34	175.32± 14.25	130.843±12.120

TABLE 2.3: ELBOW KINEMATICS PER LEVEL OF INJURY (MEAN ± SD)

	FelbowC	Extelbow	FelbowS	Supelbow	Proelbow
C5 n=7	118.624± 15.864	126.714± 19.974	111.632± 27.046	162.411± 85.775	146.391± 17.788
C6 n=4	129.835± 10.935	145.311± 25.908	125.537± 22.501	126.215± 9.024	185.726± 58.672
C7 n=3	132.846± 6.68	145.044± 9.539	131.95± 2.635	142.297± 31.714	178.916± 39.569
C8 n=1	112.46± 13.23	151.505± 32.12	116.905±12.23	122.997± 24.12	183.384± 21.14

Positive moderate correlations have been found between kinematic variables and clinical scales in the following parameters: Self-care SCIM and Shoulder Abduction step-by-step (r=0.548, p=0.034), Self-care SCIM and Complete Shoulder Abduction (r=0.518, p=0.048), Self-care SCIM and Ulnar Deviation (r=0.551, p=0.033), UL MI and Shoulder Abduction step-by-step (r=0.547, p=0.035), Self-care FIM and Shoulder Abduction step-by-step (r=0.675, p=0.0113) and Self-care FIM and Complete Shoulder Flexion (r=0.618, p=0.0243). Results are shown in Table 2.6.

TABLE 2.4: WRIST KINEMATICS PER LEVEL OF INJURY (MEAN ± SD)

	Extwrist	**Flexwrist**	**Raddevwrist**	**Uldevwrist**
C5 n=7	57.204± 11.602	44.053± 17.086	24.878± 10.11	23.155± 11.656
C6 n=4	44.275± 21.867	47.589± 13.546	20.796± 8.173	25.851± 15.579
C7 n=3	77.045± 9.831	65.793± 8.925	36.476± 2.415	42.669± 1.238
C8 n=1	56.002± 12.02	54.004± 11.23	23.656± 11.21	34.868± 10.25

TABLE 2.5: CLINICAL SUB-SCALES SELF-CARE SCIM, UL MI AND SELF-CARE FIM PER LEVEL OF INJURY (MEAN ± SD)

	Self-care SCIM	**UL MI**	**Self-care FIM**
C5 n=7	2± 1.414	66.429± 20.999	10± 2.828
C6 n=4	3± 1.414	64.25± 17.115	13± 9.539
C7 n=3	5± 1.732	69± 19.079	12± 2
C8 n=1	8± 0	93± 0	16± 0

The metrics developed were applied to patient groups. In Figures 2.6, 2.7, 2.8 and 2.9 the results are shown averaging the values of the metrics by injury levels.

The metrics developed in this study have been applied to 15 patients, then comparing the obtained values with the clinical scales' scores. As shown in Table 2.7, strong positive correlation has been found between the metric *Joint amplitude* and the Self-care SCIM (r=0.797, p=0.000375), and between this metric and the sub-scale UL MIAbdShoulder (r=0.861, p=0.00003).

TABLE 2.6: CORRELATIONS FOUND BETWEEN KINEMATIC VARIABLES RECORDED BY VR SYSTEM TOYRA ® AND CLINICAL SUB-SCALES

	Self-care SCIM	UL MI	Self-care FIM
AbdshoulderS	r=0.548 *	r=0.547 *	r=0.675 *
	p=0.034	p=0.035	p=0.0113
AbdshoulderC	r=0.518 *	r=0.385	r=0.551
	p=0.048	p=0.157	p=0.074
FshoulderS	r=0.776 ***	r=0.714 **	r=0.476
	p=0.00067	p=0.0028	p=0.1
FshoulderC	r=0.74 **	r=0.712 **	r=0.618*
	p=0.0016	p=0.0029	p=0.0243
Udwrist	r=0.551 *	r=0.336	r=0.165
	p=0.033	p=0.221	p=0.59

* p<0.05, **p<0.01, ***p<0.001

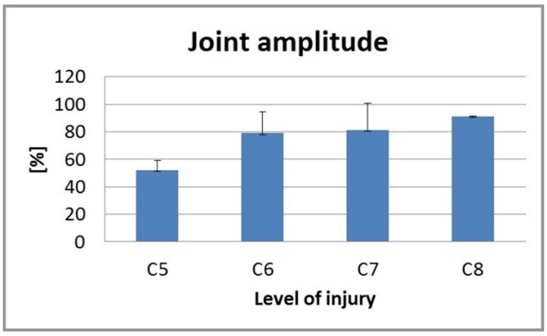


Fig 2.6 Kinematic metric *Joint amplitude* per level of injury (mean ± SD). It is expressed as a percentage with respect to the reference value of healthy subjects.

There were moderate positive correlations between the following parameters: *Joint amplitude* and Self-care FIM (r=0.591, p=0.0335), *Reaching Amplitude (Y-axis)* and Self-care FIM (r=0.708, p=0.00673), *Reaching Amplitude (Z-Axis)* and UL MI (r=0.552, p=0.0457), *Reaching Amplitude (Z-Axis)* and UL MIAbdShoulder (r=0.551, p=0.0332),

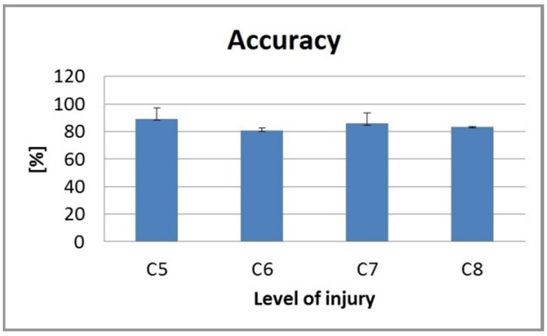


Fig 2.7 Kinematic metric *Accuracy* per level of injury (mean ± SD). It is expressed as a percentage with respect to the reference value of healthy subjects

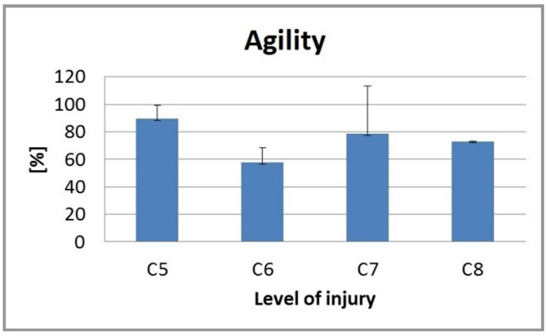


Fig 2.8 Kinematic metric *Agility* per level of injury (mean ± SD). It is expressed as a percentage with respect to the reference value of healthy subjects

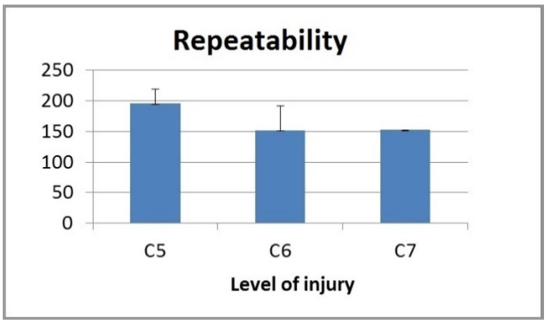


Fig 2.9 Kinematic metric *Repeatability* per level of injury (mean ± SD). It is expressed in absolute value. It has been calculated only for levels C5, C6 and C7 because the number of registers for C8 level was not sufficient to establish a reliable value. For the same reason, the reference value of healthy subjects has not been calculated for this metric.

TABLE 2.7: CORRELATIONS BETWEEN KINEMATIC METRICS AND CLINICAL SUB-SCAES

	Self-care SCIM	**UL MI**	**UL MI AbdShoulder**	**UL MI Flexelbow**	**UL MI Pinch**	**Self-care FIM**
Joint amplitude	r=0.797 ***	r=0.513	r=0.861 ***	r=0.292	r=0.276	r=0.591 *
	p=0.000375	p=0.05	p=0.00003	p=0.291	p=0.32	p=0.0335
Reaching amplitude (total)	r=-0.068	r=0.376	r=-0.041	r=-0.024	r=0.346	r=0.539
	p=0.811	p=0.167	p=0.883	p=0.931	p=0.207	p=0.057
Reaching amplitude (X-axis)	r=-0.374	r=0.05	r=-0.393	r=-0.23	r=0.14	r=0.019
	p=0.17	p=0.858	p=0.147	p=0.409	p=0.0619	p=0.952
Reaching amplitude (Y-axis)	r=0.217	r=0.4	r=0.258	r=0.005	r=0.315	r=0.708**
	p=0.17	p=0.139	p=0.354	p=0.986	p=0.252	p=0.0067
Reaching amplitude (Z-axis)	r=0.474	r=0.523 *	r=0.551 *	r=0.52 *	r=0.315	r=0.681*
	p=0.075	p=0.0457	p=0.0332	p=0.0467	p=0.252	p=0.01
Accuracy	r=-0.239	r=-0.174	r=-0.364	r=-0.442	r=-0.062	r=-0.283
	p=0.391	p=0.535	p=0.182	p=0.099	p=0.828	p=0.349
Agility	r=-0.259	r=-0.248	r=-0.536 *	r=-0.463	r=-0.081	r=-0.338
	p=0.351	p=0.373	p=0.0397	p=0.082	p=0.775	p=0.26

* p<0.05, **p<0.01, ***p<0.001

Reaching Amplitude (Z-Axis) and UL MIFlexelbow (r=0.52, p=0.0467) and *Reaching Amplitude (Z-Axis)* and Self-care FIM (r=0.681, p=0.01).

There was also a moderate negative correlation between *Agility* and UL MIAbdShoulder (r=-0.536, p=0.0397).

5. DISCUSSION

The present study shows that the kinematic data recorded by the VR system Toyra ® correlate with the clinical sub-scales more related with upper limb function, what is in line with our group preliminary results [45]. Some metrics have been defined based on these kinematic data, showing promising results in terms of clinically relevant information, as has been demonstrated by the correlation found between some of the metrics and the self-care sub-scales.

This study supports the use of such VR systems not only as rehabilitation tools but also as an objective assessment tool of the user's performance, providing data with potential clinical relevance. The different degree of correlation found between the clinical scales and the kinematic variables yields interesting information that can be used in two directions. One is to analyse in minute resolution the patients' physical state, trying to use this information to complement the clinical scales scores and to design treatments that encourage the training of the joints more linked with a functional improvement. The second direction would be to develop predictive models that could offer to the clinician an estimation of the clinical scale score expected for a patient, thus adding objective data that could facilitate the evaluation and to follow the progression of a patient. Some previous studies go in this direction [2], [67].

The highest positive correlation between clinical scales and kinematic variables was found in the step-by-step shoulder flexion. As previously mentioned, the step-by-step kinematic variables require higher muscle control, and this could be the reason of the high correlation of this variable with the functionality. Together with the moderate correlations found in the shoulder abduction, this results suggest the importance of the shoulder range or movement in patients with SCI, what is consistent with previous studies that established that shoulder muscle strength, in patients with tetraplegia, is an important determinant of functional ability level [68].

In a previous study in which correlations between kinematics and clinical scales were also studied [46], no correlation was found between shoulder range of motion and any clinical scales. However, the methodology used in that study is quite different than the one presented here, because the patients performed only one kind of reaching and grasp task, without using any VR system, so that they did not encourage them to reach their maximum values of range of motion in all directions. In contrast with that study, here the patients carry out a wide variety of tasks, because the goals to reach are displayed in some different locations around the patient. This is one of the advantages of VR, which permits to measure the patient's kinematics during different tasks without the difficulties of setting up a new physical environment for each one.

The only kinematic variable not related with the shoulder that showed positive correlation with clinical scales was the ulnar wrist deviation. This result could be due to the tenodesis effect, an anatomical consequence of the SCI very common in patients with level of injury C6 or C7 that entails a high wrist range of motion during the execution of the Activities of Daily Living (ADL) [69].

Regarding the kinematic metrics developed in this study, the higher correlation obtained between the *joint amplitude* and the clinical scales, in comparison with any of the correlations obtained between the same scales and the isolated kinematic variables, suggests that the combination of kinematic variables could offer more clinically relevant information than each individual parameter.

The strong positive correlation between *joint amplitude* and the SCIM scale, and also the Upper Limb Abduction Shoulder sub-score shows that this metric could be a good indicator of functionality. A similar result was obtained in [67], where the range of motion was found to affect to a large extent to the performance of a model that predicts the clinical score from the kinematic recordings of a therapeutic robotic arm.

Reaching amplitude along the Z-axis shows moderate correlations with four of the clinical scores or sub-scores (UL MI global, UL MI Abdshoulder, UL MI Flexelbow and Self-care FIM scale). As has been defined, the Z-axis goes vertically upwards, so that the movements in this direction require a higher force, and, thus, this ability could be closely related to the clinical measurements. Also *reaching amplitude* along the Y-axis shows a positive correlation with Self-care FIM scale. The Y-axis was defined horizontally, perpendicular to the screen, and it is thereby the direction in which some of the ADL considered in the FIM scale take place, like eating or grooming. This could be the rationale of this correlation.

The negative correlation that showed the *Agility* with the UL MIAbdShoulder was unexpected, and it could indicate that the normalization by the mean velocity used to calculate this metric may have not been enough to counteract the presence of involuntary movements, very common in patients with SCI, that usually lead to the appearance of high velocity peaks. Further filtering strategies and an optimization of the metric's parameters will be necessary to improve this metric.

In respect to the metric *accuracy*, no correlation with clinical scores was found, in contrast with a previous report, where there were strong correlations between a metric called "trajectory error", with a similar foundation to the *accuracy* presented here [70]. We believe that the clinical scales (Self-care SCIM, Self-care FIM and UL MI) used in our study do not encompass the specific information that this metric provides. Maybe other methods could be used in further researches to evaluate its validity. For example, in the mentioned study, clinical scales Fugl–Meyer, Motor Activity Log, Action Research Arm Test, and Jebsen-Taylor Hand Function Test were used. These scales are likely to measure aspects more related to the accuracy of movements than the ones used here.

These metrics present some limitations, such as the different number of patients in each group of injury. Therefore, it will be necessary to increase the number of patients in future research, in order to have a sufficient number to compare the averages of each level of injury. It could be also interesting to apply this metrics and kinematic analysis when the patients are performing more functional task such as ADLs in VR environments, not only analytical movements as in the Evaluation session presented here.

6. CONCLUSIONS AND MAIN CONTRIBUTIONS

1. A new set of kinematic metrics to evaluate upper limb function by means of a virtual reality rehabilitation system has been designed.
2. Clinical key features have been translated into mathematical formulations that comprise the kinematic data recorded by the inertial sensors.
3. It has been shown that some of the defined kinematic metrics are correlated with standard clinical scales, therefore proving its clinical meaning.
4. The set of kinematic metrics provides objective information of clinical relevance that allows patient segmentation, as well as a more accurate assessment, which is essential to facilitate the use rehabilitation technologies in clinical settings.

5. These metrics, together with the virtual reality system, offer the possibility of carrying out evaluation and therapy simultaneously, which is very important to refine patient’s treatment.
6. A method to minimize the influence of involuntary movements in the assessment of the agility has been defined by considering the relationship between the mean and the maximum angular velocity.
7. In comparison with previous works, this is one of the first studies that have found clinically relevant information in a virtual environment of rehabilitation, gathering parameters from a complex and varied set of exercises performed by SCI patients.

CHAPTER 3: BRAIN-TRIGGERED ELECTRICAL STIMULATION WITH VIRTUAL REALITY FEEDBACK IN PATIENTS WITH INCOMPLETE SPINAL CORD INJURY

1. INTRODUCTION

The prevalence of spinal cord injury (SCI) is 223–755 per million inhabitants, with an incidence of 10.4–83 per million inhabitants per year [39]. In one third of the patients, the SCI is reported as tetraplegic, in which the arm and hand functions are affected to a different degree, depending on the level and severity of the injury [71]. One of the greatest needs to improve the quality of life of patients with tetraplegia is the improvement in upper extremity function [41] and, in particular, the recovery of grasping has been identified as the priority for most subjects [72].

In this context, one of the therapies for the recovery of grasping is functional electrical stimulation (FES), which is aimed to drive impaired muscles and joints using electrical pulses to execute predefined functional tasks. There are studies supporting the benefits of FES in recovery of upper limb function, like grasping in SCI patients [73].

It is crucial for the success of the FES therapy to apply the electrical stimulation while the patient is volitionally attempting to perform the movement. In fact, it has previously been shown that the effectiveness of FES when applied without patient's voluntary involvement is reduced by approximately half [74]. This volitional trigger is currently achieved by different methods, such as residual electromyographic activity [75] or gyroscopes [76]. However, these methods present several shortcomings, since very often SCI patients suffer hypertonia and involuntary movements that can cause discrepancies between the patient's intention and the movement, probably decreasing the neuroplastic effects of the therapy [12].

Brain-machine interfaces (BMI) allow the real-time decoding of neural commands (e.g., by the use of electroencephalographic signals) and therefore provide a very useful method to detect a volitional trigger. The patient's intention is identified from the ongoing neural activity and can be used to control different devices. This approach opened the door to several BMI applications which could potentially be used by SCI patients, most of them with assistive purposes. However, the potential of BMI for rehabilitation is especially relevant in patients with incomplete SCI, since it is believed that only 10% of spared neuronal pathways is sufficient to provide a functional recovery [10].

The combination of BMI and FES can be used with a rehabilitative purpose in incomplete spinal cord injury (iSCI) patients [11], relying on the hypothesis that a long-term potentiation (LTP) is induced at synapses in the spinal cord when descending signals from the brain reach the synapse at approximately the same time as antidromic volleys from the stimulated peripheral nerves [12]. From this perspective, and supported by the principle of Hebbian learning [77], a therapy based on simultaneous activation of the motor pathways (through motor intention detected by the BMI) and the sensory pathways (through functional electrical stimulation) of the corticospinal tract should have a bigger effect than both therapies alone [14].

Moreover, as a rationale for many existing motor therapies is the premise that repetitive and engaging practice using the affected limb induces plastic changes in neural networks involved in motor control and learning [15]. In this regard, feedback is a key feature during the rehabilitation therapy, since it allows the patients to feel their performance improvements along the sessions, thus engaging and motivating them, and also it permits to receive a contingent response to the motor intention. However, human musculoskeletal structures form a very complex system that presents non-linear and time-variant muscular responses to FES [16]. Therefore, patients have different muscular responses to constant values of FES, hindering the reception of a repetitive and positive feedback during the therapy. This may be compensated by including a supplementary source of feedback. The use of a virtual realistic feedback allows incorporation of an additional reward, based on the principles of gaming for rehabilitation, which may improve the adherence of the patient to the therapy [78]. Furthermore, it has been hypothesized that, since there is a larger proportion of visual fibers entering to brain structures responsible of learning, visual feedback may lead to faster learning [18]. Indeed, there is a recent study that showed significant recovery of locomotion in SCI patients after 12 months of training with a combination of BMI, exoskeletons and virtual reality feedback [19].

BMIs in combination with FES and VR also provide the possibility of evaluating patient’s progress during the rehabilitation process. This can be achieved by analyzing EEG signals recorded during the sessions and computing algorithms to measure functional connectivity

(FC). This topic will be addressed during Chapter 4, and therefore it will not be explained during this chapter, but it is important to keep it in mind, because this aim was also present during the design of the system.

For all these reasons, we believe that the integration of the aforementioned technologies into a single system, easy to use and safe for the patients, is essential to fill the existing gap between research studies and clinical studies in the BMI field. Before getting to a clinical study to assess the effectiveness of a technology-based therapy, it is crucial to carry out a pilot evaluation of the system in a real clinical environment, in order to test the system performance and its immediate effects on the patients. Therefore, the objective of the present work is to investigate if the closed-loop feedback system resulting from the integration of BMI, FES and virtual reality feedback can be used for hand rehabilitation by iSCI patients, in a clinical setting, safely and comfortably for the patient. To this end, the first step was to design a system that fulfilled all the requirements that will be further explained in the Methods section. Then, an initial pilot system was tested with 3 healthy subjects to refine the characteristics, especially those concerning the EEG classifier. After redefining the system and checking its proper performance with healthy subjects, a pilot pre-clinical experience with 4 iSCI patients was carried out to evaluate the feasibility of the system in a clinical environment.

2. STATE OF THE ART

As we have mentioned in the introduction, most of previous BMI studies have focused on the development of assistive devices for people with complete injuries [79][80][81]. However, the approach of this study is slightly different, since the objective is to design a device that could be used in the daily rehabilitation of patients.

Indeed, a large body of literature supports the benefits of systems triggered by neurophysiological commands to promote motor recovery in stroke patients [20][82][21][22] as well as neuroplasticity in healthy subjects [23]. Nevertheless, there are fewer studies that apply these systems to SCI patients. In a recent study, BMI+FES were applied to SCI patients with both complete and incomplete injuries (ASIA [24] A and B, respectively) with a rehabilitative aim, obtaining moderate improvements in functional outcomes of the patient with ASIA B, and no changes of the patient with ASIA A [25]. In another study, BMI+FES were applied to partially recover gait function in a patient with SCI [26]. More recently, a study with SCI patients has shown that BMI+FES restores Event-related Desynchronization (ERD) cortical activity and muscle strength to a higher extent than passive FES [27]. The feasibility of the combination of BMI and exoskeleton for lower limb rehabilitation has been also tested in SCI patients [28]. However, it remains unclear if training with BMI+FES may induce functional gains; therefore, in our study we assess functional status before and after the training by means of clinical scales.

3. METHODS

3.1) Introduction

Since there are not many examples of similar systems implementing BMI systems in clinical environments, several challenges must be addressed both during the design and the experimental stages. The final aim is to design a system for neurorehabilitation that could be used by SCI patients in their daily rehabilitation. Therefore, we defined the following requirements:

- Safety: this is the most important criteria to follow and, hence, it affected mostly the integration stage and specially the FES subsystem, since this is the one that could be potentially more dangerous for patients.
- Balance between time and efficacy: since patients have a very tight schedule during their inpatient hospital stay in a rehabilitation center, the time for preparation of the system must be as short as possible, and must be accompanied by a clinical improvement that could make worthwhile the time invested during the realization of the therapy. Although the demonstration of the clinical efficacy of this experimental therapy is out of the scope of this work, since this is a first approach with a small number of patients, a clinical evaluation was performed to all of them to obtain first insights of the potential benefits of the use of this system.
- Accuracy: a value over 70 % of correct results is generally considered acceptable for a BMI [83]. Moreover, for a BMI intended to be used for clinical

therapy, we believe that it should be slightly higher, to avoid frustration in the patients when receiving a feedback that could be incongruent with their intentions.

- Delay: this is another essential feature, since, to guarantee the success of the therapy, it is crucial that patients feel that they are controlling both the VR and the FES device from their own thoughts. If the delay between the motor attempt (MA) and the appearance of the feedback is too long, it could affect the neuroplastic reinforcement provided by Hebbian learning, as it was previously explained in the introduction of this chapter. The delay constraint was specially taken into account during the choice of the communication protocol between the controller and the different devices.
- Robustness: it is mandatory to design a system robust against failures, because, as we have already mentioned, the time available for the therapy is very scarce and, therefore, interruptions must be minimized.
- Usability: in order to obtain a device that could be potentially used in the daily rehabilitation, we have to ensure that patients are willing to use it. This requirement is difficult to quantify, since it is subjective and comprises several other aspects previously described, such as delay, robustness, efficacy, etc. It is necessary to keep this idea in mind during the design of the system, because a balance should be found between complexity and capability. For example, when detecting the motion intention of the patients, the more the number of sensors used, the better the accuracy will be, but increasing the number of sensors could affect patients' comfortableness. Hence, this requirement will be present along the whole process of designing and testing the system. With the aim of evaluating the usability of the designed system, a test was fulfilled by every patient after performing 5 sessions. This kind of studies add valuable information to the state of the art, since most of BMI studies have been conducted by healthy subjects without taking into consideration the needs of the final users.

Along the following sections, we will firstly explain the description of the different subsystems that were designed and integrated in this study, as well as the process carried out to decide which technological solutions were the most appropriate according to the defined requirements.

3.2) Description of the system

We designed a system for neurorehabilitation, comprising a BMI that decoded the patient's intention in real time and triggered the other 2 subsystems simultaneously: FES and virtual reality feedback. The virtual reality feedback was displayed on the screen at the same time that the grasping was generated. It consisted of a virtual open hand that closed when the patient's motor intention was detected. The system designed in this work consisted of the following subsystems, as can be seen in Fig. 3.1 a:

1) Brain-machine interface.
2) Functional Electrical Stimulator (FES).
3) Virtual reality feedback and graphical user interface.
4) High Level Controller (HLC).

Each of these subsystems will be further described in the following subsections.

3.2.1) Brain-machine interface

a) EEG Recording

The EEG was acquired using a commercial g.Tec system (g.Tec GmbH, Graz, Austria), with 32 channels placed at AFz, FC3, FCz, FC4, C5, C3, C1, Cz, C2, C4, C6, CP3, CP1, CPz, CP2, CP4, FP1, FP2, F7, F3, Fz, F4, F8, T7, T8, P7, P3, Pz, P4, P8, O1, and O2 (according to the international 10/10 system, see Fig 3.2). The ground and reference electrodes were placed on FPz and on the left earlobe, respectively. The EEG was digitized at a sampling frequency of 256 Hz, and power-line notch filtered to remove the 50 Hz line

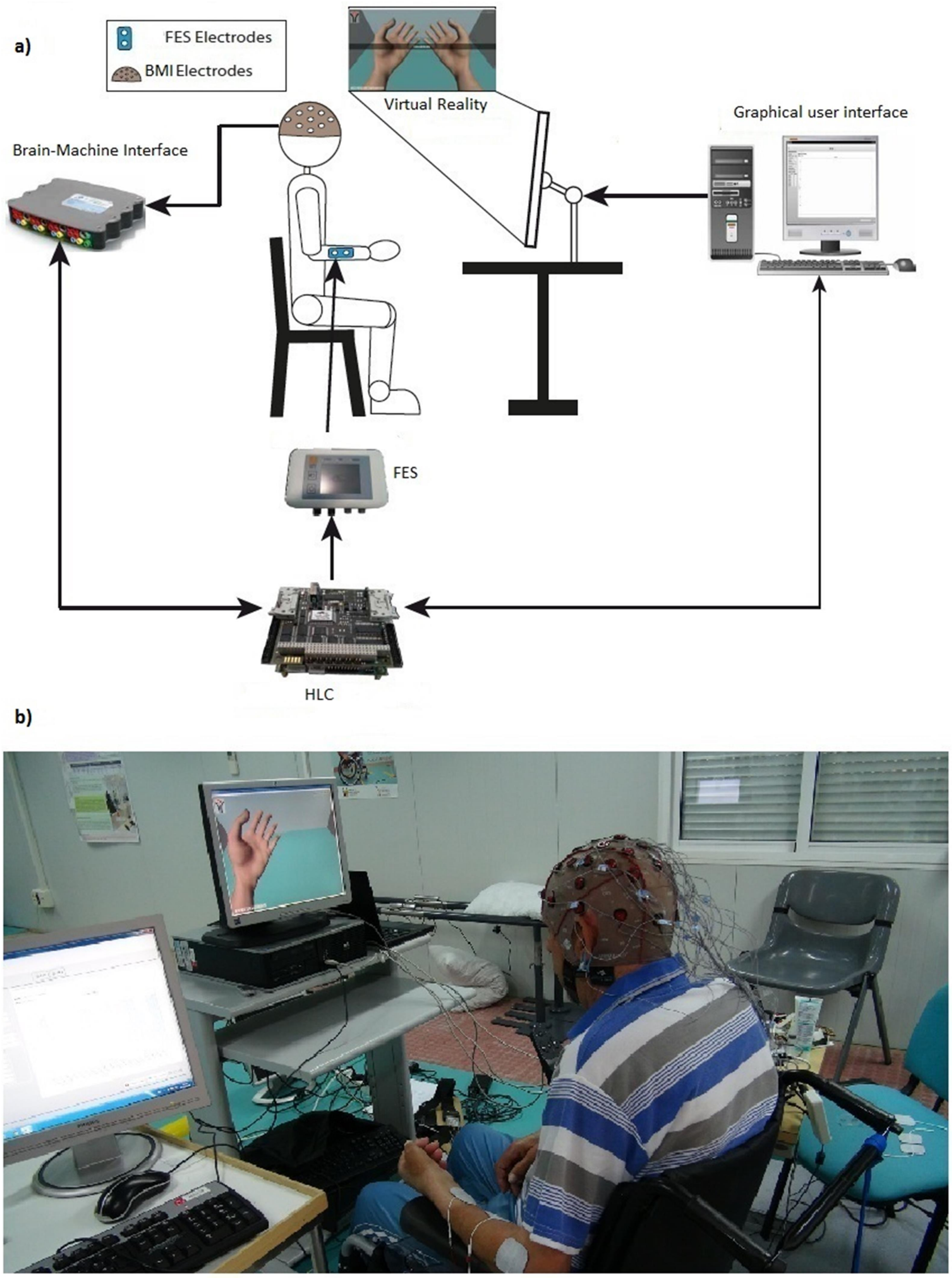


Fig 3.1 (a) General architecture of the BMI+FES system for therapy (b) Patient carrying out a session.

interference. Although we believe that fewer channels could be sufficient to achieve an acceptable accuracy to control a BMI, we decided to choose 32 channels because we will use this information to develop algorithms to compute neuroplasticity metrics that will be described in Chapter 4. Once these metrics are defined, a smaller number of channels could be sufficient in future experiments with the systems.

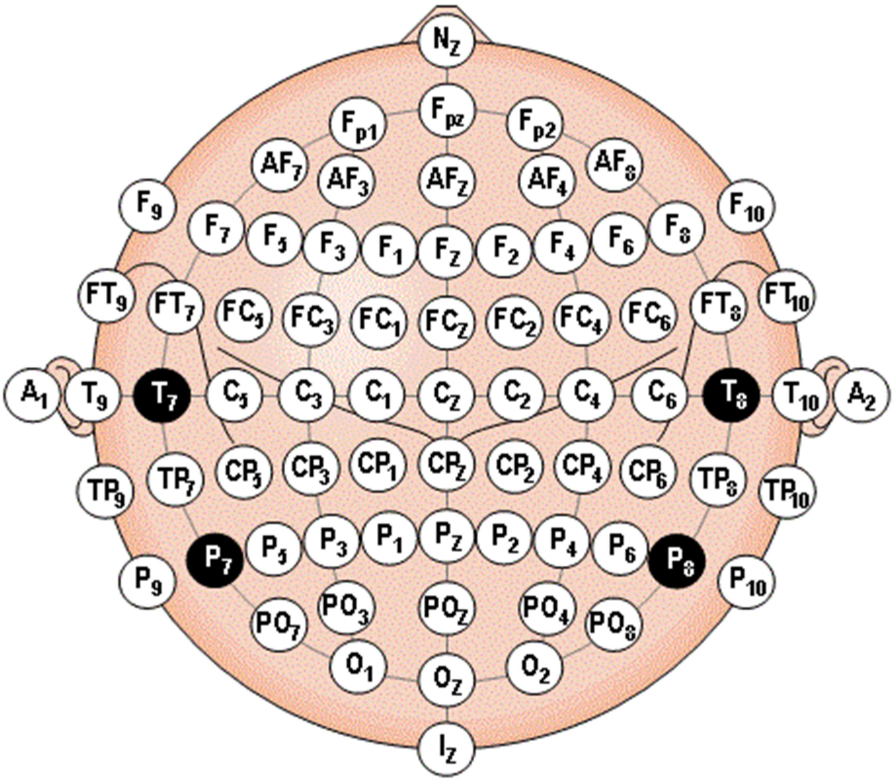


Fig 3.2 International standard 10/10 for EEG recordings (redrawn from [84])

The aforementioned EEG recording system requires the use of a conductive gel to maintain a proper contact between the skull and the electrodes. Although there are already available EEG recording systems with dry electrodes, their efficacy has not been yet completely shown, and, therefore, it will be a matter of future researches to determine if BMI-based therapies can be implemented with dry electrodes. That would be the ideal situation, since it would dramatically decrease the preparation time as we as the discomfort for the patient and the need of washing them after the experiments, which adds additional burden to the caregivers, as it has been identified by previous authors [85].

Bearing in mind these considerations, we tried to minimize as much as possible the required time for preparation. To this end, we developed an easy-to-interpret graphical interface that shows with different colors which electrodes have proper impedance (below 5 kΩ) and which not. This is helpful for the clinicians and allows the system to be used by therapists who do not have previous experience with EEG.

With this setup, we obtained preparation times below 15 minutes for every session, which was within our expectations.

b) EEG signal preprocessing

A z-score procedure was applied to remove artifacts. It consists in automatically discarding trials whose δ power (1-4 Hz), θ power (4-7 Hz), α power (7-12 Hz), β power (12-30 Hz), trial variance or maximum amplitude more than 2.5 times higher than the mean. It is a recursive process, since the mean is calculated again after rejection of a trial, and the z-score procedure is applied until no more trials are rejected. Other authors applied the same procedure but discarding trials with values twice higher than the mean [86], but in the case of our study, as the number of trials is not so high, we used a looser threshold.

Moreover, signals were bandpass filtered (between 0.1 and 50 Hz) by means of a 10^{th} order Butterworth zero-phase shift filter, whose frequency response is shown in Figure 3.3, in order to remove DC shifts.

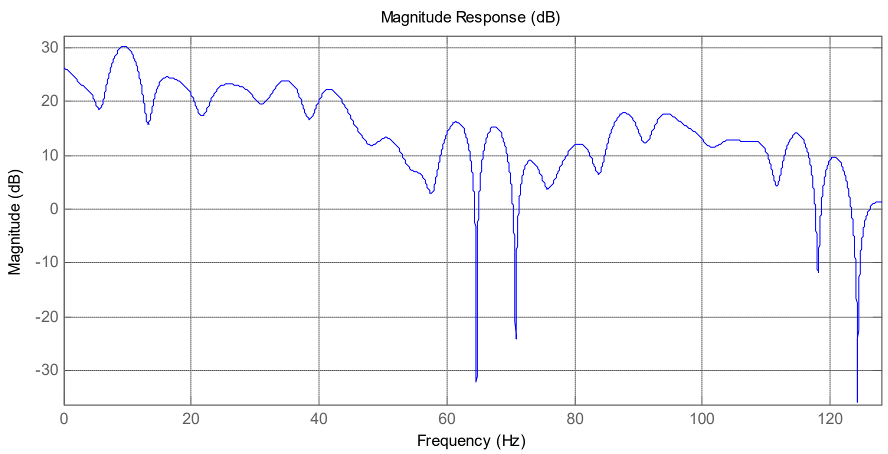


Fig 3.3 Frequency response of the Butterworth bandpass filter.

c) Feature extraction and classification

c1. Requirements

The aim of the BMI system is to differentiate between hand motor attempt and rest as accurately and fast as possible. Moreover, as the system is intended to be used in a clinical environment, there is another requirement that must be taken into account, which is the time to setup the whole setting. This time includes the training of the classifier, which involves the realization of some training sessions to record enough data, as well as the time needed to specifically train the classifier with the recorded signals. This could be a very time-consuming process, depending on the method used to classify, and a balance must be kept between acceptable accuracy and time spent. In a clinical environment, patients are always involved in a very intense rehabilitation program that makes difficult to find more than one hour to perform experiments or new approaches for therapy. Therefore, it is mandatory to design a classifier that minimizes the required time for calibration.

Another essential characteristic to be taken into account by our classifier should be the amount of information required to obtain a robust classifier: there should also be a balance between accuracy achieved and number of signals required. There is a general consensus in the BMI community about the fact that an accuracy over 70 % is regarded as sufficiently high to operate successfully a BMI [83]. For a BMI intended to be used for clinical therapy, as we have already mentioned, we believe that it should be slightly higher, to avoid frustration in the patients when receiving a feedback incongruent with their intentions.

c2. Choice of the features

We extracted two EEG movement correlates: event-related desynchronization (ERD) of sensorimotor rhythms [87], and movement-related cortical potentials (MRCP) [88].

ERD/ERS is the task-related or event-related change in the amplitude of the oscillatory behavior of specific cortical areas within various frequency bands [89]. An amplitude (or power) increase is defined as event-related synchronization (ERS), while an amplitude (or power) decrease is defined as event-related desynchronization (ERD). As event related potentials, ERD/ERS patterns are associated with sensory processing and motor behavior, when neurons are in a resting state, they have a fixed potential. But then, when an action is being prepared, neurons begin to activate at different instants, so they add each other in a destructive way, leading to a global decrease of the power. When neurons accomplish the task, they return to the resting state, staying ready for the next task. This produces a new synchronization of neurons, globally working as an increase of the power. This phenomenon is frequency-dependent, so it is necessary to use metrics such as power spectral density to detect it, as can be seen in the figure 3.4. An important characteristic of the ERD/ERS is that they appear both when the subject imagines or attempts to move and when he/she actually moves. This makes them very useful in the context of a BMI and, therefore, they have been very often used.

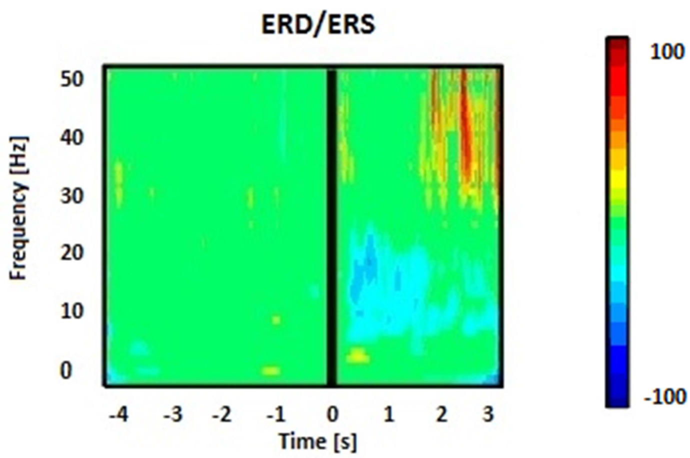


Fig 3.4 Representative time-frequency power spectral density map of the ERD/ERS at C3 electrode from a patient of the study,
where t=0 is the cue arrival.

MRCP are slow cortical potentials and they also happen when the subject volitionally initiates, attempts or imagines a movement. They are amplitude features, as can be seen in the figure 3.5.

ERD/ERS and MRCP were chosen because both of them present several advantages for their use in BMI within a clinical environment:

- They are measurable even in paralyzed patients [90], [91].
- They allow high temporal precision when using robotic prostheses [92].

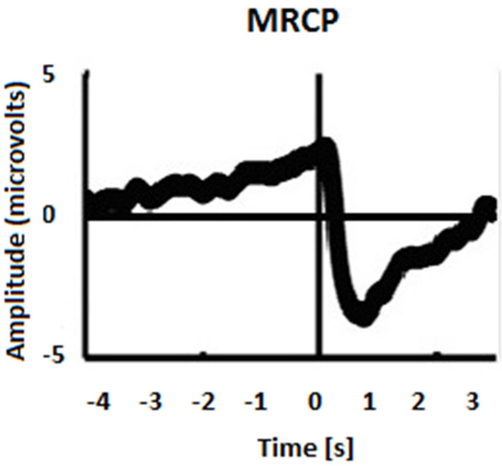


Fig 3.5 Representative amplitude of the MRCP at C3 electrode from a patient of the study, where t=0 is the cue arrival.

More specifically, MRCP present additional advantages that make them a suitable feature for BMI applications in a clinical context:

- They are more stable between subjects and days, therefore, they require less training, which is an essential requirement, as we have already commented.
- They can be detected faster than sensory-motor rhythms, presenting detection delays of hundreds of milliseconds [93], [94].
- They can be elicited even by naïve users, in contrast with sensory-motor rhythms, where between 20 and 25 % of subjects are not able to generate detectable signals [95].

There is also an important disadvantage that must be considered, which is their low amplitude, making them more sensitive to noise. For example, eye movement presents a similar shape than MRCP and higher amplitude, but this inconvenient was addressed by using a common average reference (CAR) filter to compute the MRCPs, which will be further explained. ERD and MRCP calculation process will be described in the following subsection "Feature extraction".

Therefore, we have identified these 2 features as suitable candidates for a BMI system in a clinical environment. A previous study showed that the combination of the two kinds of features achieves better results than separately in stroke patients for movement intention decoder [96]. The novelty of this study is that both of them are going to be applied in an online BMI with SCI subjects.

c3. Feature extraction and classification

After identifying the frequency bands to be used, we chose the sliding window length. One second window was chosen as an ideal value, because it allows extracting frequencies between 1 Hz and 128 Hz, so we are covering the spectrum needed for the ERD features. For the MRCP it is not needed to cover any spectrum, since this an amplitude feature.

Subsequently, we had to design an ideal time step for the sliding window that matches the aforementioned requirements. A too short time could prevent the system to work in real-time, since time for feature calculation for each window could be higher than step time. Also, a too long time could cause a considerable delay between the patient's motor intention and the system response. Therefore, an appropriate balance must be found. Firstly, we tested with healthy subjects a sliding step of 125 ms, but the response of the system was too slow. Subsequently, a sliding step of 62.5 ms was tested and it worked properly in real-time. The delays between the appearance of the cue and the response of the BMI+FES+VR system obtained from 3 healthy subjects with these characteristics are shown in the table 3.1. They have been calculated averaging 40 trials carried out by each subject.

TABLE 3.1: Average delays obtained by healthy subjects.

Subject 1	**Subject 2**	**Subject 3**
0.92 s	1.15 s	1.02 s

It is important to emphasize that these delays have been computed from the appearance of the cue to the response of the system, it is not the delay between the beginning of the motor attempt and the response of the system, which would be considerably shorter. These delays were considered as acceptable, since they were short enough to provide the subjects a feeling of natural and uninterrupted control of the system.

Therefore, after testing with healthy subjects, the final configuration was achieved, with a one-second long sliding window applied with a sliding step of 62.5 ms between -4 and -1 seconds to represent the rest class, and between 0 and 3 seconds for the MA class (with 0 being the time of the presentation of the MA cue), as can be seen in Fig. 3.6.

Fig 3.6 Paradigm used for the interactive sessions with the BMI + FES + VR, where t=0 represents the cue appearance

For each 1-second window, ERD and MRCP features were extracted:

• ERD features were extracted after applying a small Laplacian filter to the fronto-central (FCx), central (Cx), and centro-parietal (CPx) EEG channels. Then, a 16th order autoregressive (AR) model with a frequency resolution of 1 Hz was used to obtain the power values in the frequency range [7-30] Hz, based on Burg's algorithm [97], according to

$$y_E[n] = \sum_{k=1}^{16} a_k \cdot y_E[n-k] + e[n], \qquad (1)$$

where y_E denotes the electrode of interest and *e[n]* is the error with zero means and variance σ^2. This method computes the AR coefficients a_k by minimizing the sum of the square of the forward and backward prediction errors, thus reducing the minimum entropy components, which are generally associated to noise [98]. Power spectral density (PSD) is calculated from the AR coefficients using the following expression:

$$P(w) = \frac{\sigma^2}{|1 - \sum_{k=1}^{16} a_k e^{-ikw}|} \qquad (2)$$

As the number of EEG channels used was 15 and the number of frequency bins (between 7 and 30 Hz, with a resolution of 1 Hz) was 24, the total number of ERD features extracted for each 1-second window will be 360.

- MRCP features were computed after subsampling the signals to 64Hz and applying a bandpass filter between [0.1-1] Hz. Subsequently, a common average reference (CAR) was applied to channels FC3, FCz, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2, and CP4, whose time samples were added to the features vectors. As the number of EEG channels used was 13 and the number of samples is 64, there will be 832 MRCP features for each 1-second window.

Hence, for each window, a total of 1192 features were extracted.

A sparse discriminant analysis (SDA) was used to automatically select the most discriminant features, after removing redundant ones [99]. SDA is based on the classical Lineal Discriminant Classifier (LDA), which is a well-known method, commonly used in the BMI field, favoured due to its simplicity, robustness and high accuracy in low-dimensional settings. However, it can fail when the number of features is higher than the number of observations, as is the case of our study. Hence, it may be desirable to perform the classification with just a subset of the predictors (features). This is called a sparse classification and ensures an easier interpretation of the model as well as reducing overfitting. With this aim, Sparse Discriminant Analysis (SDA) was developed by Clemmensen *et al.*[99]. This algorithm performs simultaneously feature selection and classification. It also reduces noise by using 2 constraints to the classifier that estimate some of the classifier weights as exactly zero. Therefore, SDA works as a penalized version of LDA. SDA has been used in different domains of machine learning field, but it has not been so broadly used in the BMI context. Therefore, we believe that this algorithm could be very useful for BMI applications, since it reduces the training time for the classifier and it is especially appropriate when the number of features is higher than the number of observations.

In this paper, as in Clemmensen *et al.* work, we are using the optimal scoring formulation of the LDA classifier, that manages the classification problem as a regression problem by turning the categorical variables into quantitative variables [99]. This conversion is performed by means of a vector (θ_k) that assigns scores to the different classes. Adding the

2 aforementioned constraints to achieve sparseness, the SDA algorithm gives the solution to:

$$\text{minimize}_{\beta k,\theta k} \{||Y\theta_k - X\beta_k||^2 + \gamma\beta_k^T \Omega\beta_k + \lambda||\beta_k||_1\}, \qquad (3)$$

subject to 2 constraints to prevent trivial zero solutions:

1) $\frac{1}{n}\theta_k^T Y^T Y\theta_k=1$, to obtain vectors that are normalized with respect to an inner product.
2) $\theta_k^T Y^T Y\theta_l=0 \ \forall \ l<k$, to obtain mutually orthogonal vectors.

In the following lines we will describe the meaning of each symbol:

- *Y* is a *nxK* matrix of dummy variables (where *n* is the number of samples and *K* the number of classes), indicating Y_{ij} elements whether the ith observation belongs to the jth class.
- θ_k is the score vector *(Kx1)* that assigns scores to the different classes. It must be centered and with unit variance.
- *X* is a *nxp* matrix of observations, where *n* is the number of samples and *p* the number of features.
- β_k are the discriminant vectors.
- *Ω* is the penalty matrix. It must be positive definite and it is defined as $\Omega = \frac{1}{n} Y^T Y$.
- γ is a non-negative parameter that controls the smoothness of the discriminant vectors.
- λ is a non-negative parameter that controls sparseness of the discriminant vector. It assigns zero weights to some of the features in order to reduce dimensionality.

Although for each subject and sessions this feature selection process will be repeated, it is necessary to establish the same number of features for all of them. Therefore, at each session, the classifier could make use of a different subset of features, but with the same size in all of them. In order to find the optimal number of features, we performed an offline analysis with the data obtained from 3 healthy subjects. γ and λ are the tuning parameters that determine the smoothness and the sparseness of the discriminant vectors. It is also necessary to determine the number of features that will be used. With this aim, we firstly performed an initial optimization process, with a fixed number of features, selected as 50. We performed a 5-fold cross-validation test, training and testing the classifier for each subject with different combinations of γ and λ. For γ, the interval of possible values ranged between 10^{-7} and 1000 in a logarithmic scale. For λ, the interval ranged between 1 and 40 in a linear scale. We show in the figure 3.6 the accuracies obtained with the different feature combinations for different number of features. We show in the table 3.2 the five parameter combinations that maximized accuracy.

TABLE 3.2: Results of the five combinations of SDA parameters that maximize accuracy with 50 features.

Combination of parameters	γ	λ	**Accuracy**
1	10^{-5}	15	90.1 %
2	10^{-3}	20	89.3 %
3	10^{-5}	13	89.1 %
4	10^{-6}	11	88.7 %
5	10^{-4}	12	87.2 %

We wanted to analyze if the accuracy remained stable when decreasing the number of features. With this aim, we tested with the 5 aforementioned combinations of parameters, but changing the number of features. We show in the figure 3.6 the results, where it can be seen that accuracy dramatically increases from around 18 features, but then it stabilizes around 30. Therefore, 30 was chosen as the number of features that will be used with patients.

On each session, the movement intention decoder was calibrated after recording the screening blocks, and used in real-time during the closed-loop feedback blocks. Its objective was to distinguish between the brain signals corresponding to rest and MA. To that end, it was trained specifically for each patient using all the trials from the screening blocks recorded in previous, as well as in the same session, with that patient.

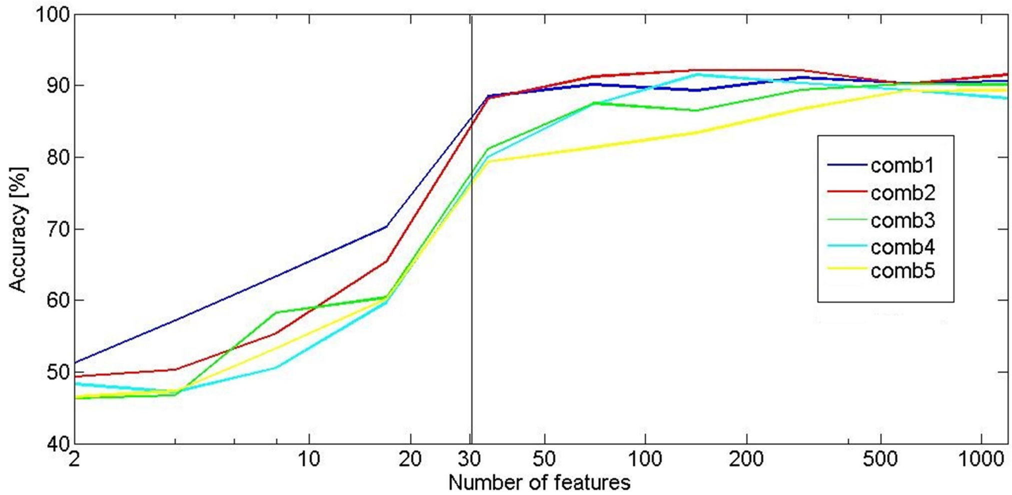


Fig 3.6 Average accuracies obtained by healthy subjects with different number of features and the five best configurations of SDA parameters.

c4. Decoding scheme

During the online operation of the system (i.e., for the feedback blocks) the EEG was monitored continuously. A sliding window was applied every 62.5 ms, extracting the features previously described, and keeping the values selected by SDA. For each sliding window, the BMI classifier determined if the signal corresponded to rest or to MA class. When five consecutive windows of MA class were detected, the BMI sent a trigger to the high-level controller. The controller ignored the BMI outputs during the rest periods to avoid stimulating the patients due to false detections. Therefore, on each feedback trial, the patient was stimulated if the BMI generated a trigger after the "Movement" cue appearance.

3.2.2) Functional electrical stimulator

The INTFES stimulator (Technalia S.L., Spain) was used to drive grasping movement synchronized with the patients' intention to move. The forearm flexor muscles (Flexor

Carpi Ulnaris, Flexor Digitorum) were superficially stimulated through a pair of electrode pads (Pals Platinum – rectangle 2'' x 2''). A common reference electrode was placed near the elbow. A clinician set the stimulation parameters before the first session, using a biphasic pulse of 40 Hz with 350 µs of duration for all patients. The pulse amplitude was set independently for each patient and gradually increased until the grasping response was generated within comfortable limits. Amplitude was adjusted before each session to compensate time-varying muscle response, although it was changed only once, before the second therapy session of subject S2, when amplitudes of Flexor Digitorum and Ulnaris electrodes were decreased, due to the discomforts reported by the patient. The amplitude parameters used for each subject are shown in the table 3.3.

TABLE 3.3: FES parameters for each subject.

Subject	Amplitude of Flexor Digitorum electrode	Amplitude of Flexor Ulnaris electrode	Stimulated hand
S1	26 mA	19 mA	Left
S2	19 mA (*)	16 mA (*)	Left
S3	25 mA	26 mA	Right
S4	18 mA	14 mA	Right

(*) In the second session of S2, Amplitude of Flexor Digitorum and the Ulnaris electrodes were decreased to 9 mA and 6 mA, respectively

3.2.3) Virtual reality feedback

The main purpose of this subsystem was to provide a realistic feedback to the patient, consisting of a hand closing, triggered by the BMI when the motor intention was detected. The hand was displayed in a first person perspective, with the background simulating the walls and the floor of the laboratory, in order to increase the feeling of immersion. The objective was to provide a positive feedback regardless of the actual movement that FES was eliciting, which can vary between patients, sessions, and even between trials of the same session. The virtual environment has been developed using open source 3D programming interface, Open Scene Graph.

There is also a graphical user interface that allows clinicians to easily input parameters for the electrical stimulator, as well as visualizing the accuracy results in real-time.

3.2.4) High-Level Controller (HLC) and architecture

The HLC is implemented in a PC104 architecture running under XPC Target® environment for real time operation. It is responsible of coordinating the therapy operation. It receives the therapy session parameters specified by clinicians, configures the FES device based on these parameters and synchronizes with the BMI system for setting up the listening and blanking signal windows. The interconnections between the different subsystems are shown in the figure 3.7.

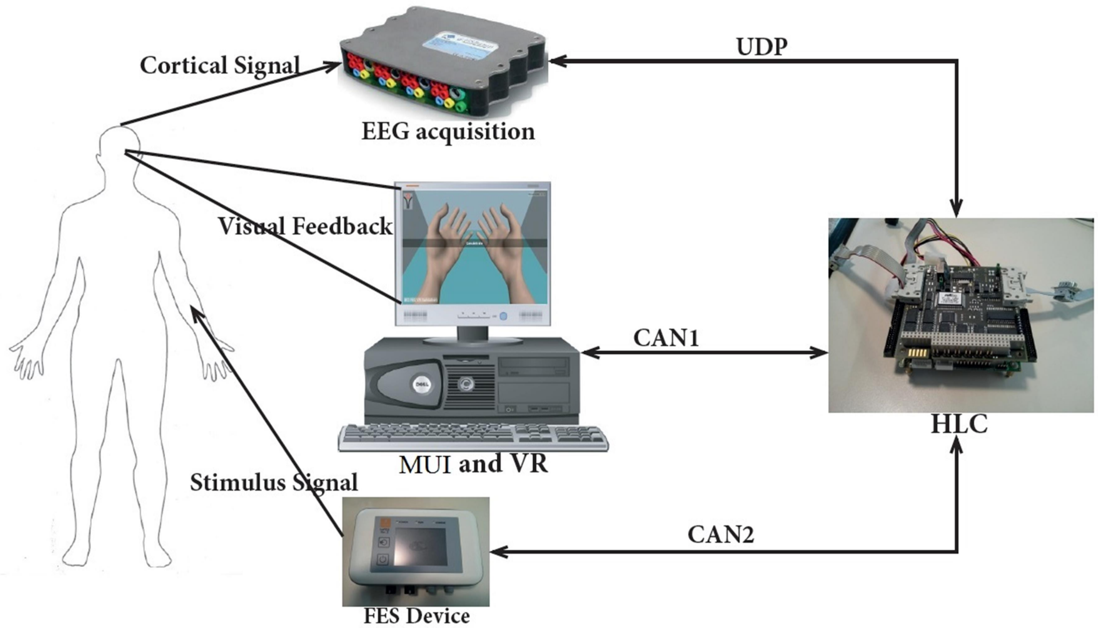


Fig 3.7 Interconnections between the different subsystems and the controller.

PC104 is an ideal platform to develop embedded systems, since it is compact, rugged and easily expandable. Therefore, it met the requirements that we previously specified for our system. `

Connection between HLC and EEG recording system was established via UDP, since we required fastness to send a constant flow of EEG data. For the communication between the VR, FES and HLC, a CAN bus was chose, because of its following characteristics:

- Robustness against interferences.
- Ability to self-detect failures.
- Ability to communicate systems from different manufacturers.
- It reduces the number of wires due to its multiplex nature.

The intervention session is composed of 4 states. The first corresponds to the "Idle" state, where the system is waiting for FES parameters, stimulation time, number of repetitions, EEG time window for signal listening and blanking and the rest periods after stimulation. Once all this information is correctly set up and all devices are connected to the HLC, the therapy starts and the system switches sequentially to other states, which are "Movement Intention Detection", "Grasping", and "Rest". During the "Movement Intention Detection" state, the EEG system is recording and analyzing signal and it sends a trigger signal when it detects a MA. When the HLC receives this trigger, the system moves to "Grasping" state (FES on) during a period of time previously established by the clinician, and then it goes to the "Rest" state (FES off). If the trigger signal was not generated, the system moves directly to the "Rest" state (FES off). This process repeats until the number of repetitions is fulfilled. The state diagram is represented in Fig. 3.8.

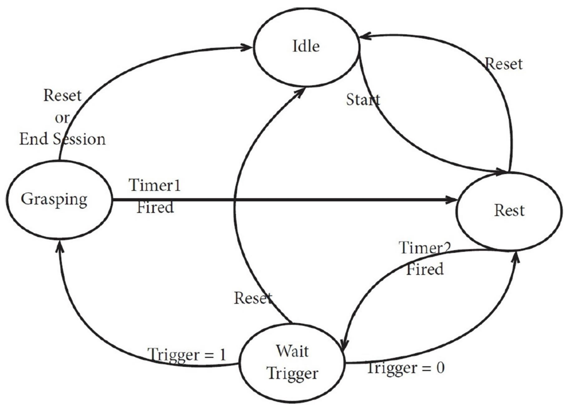


Fig 3.8 State diagram of the system.

3.3) Patients

Patients were recruited within a hospital specialized in Spinal Cord Injury and the experiments were approved by the Local Ethics Committee. Since the main objective of the intervention is to investigate the potential of the BMI+FES as a neurorehabilitation tool for the grasping function, all patients must have this movement affected, but, at the same time, to have possibilities of recovery. Therefore, we considered for the study patients able to slightly move their hand, but not able to perform grasping. These requirements lead to determine the following inclusion criteria:

(1) SCI classified as ASIA B, C or D, with cervical neurological level of injury (NLI), according to the International Standards for Neurological Classification of Spinal Cord Injury [100];

(2) to have a limited hand functionality, getting 3 or less in the Manual Muscle Testing (MMT) in the wrist and fingers muscles [101];

(3) age between 18 and 75 years;

(4) muscular response to electrical stimulation;

(5) spasticity less than 3 in the Modified Ashworth Scale [102]; and

(6) no history of osteoporosis or cardiorespiratory illnesses.

Four patients with SCI were recruited for this study. Patients' information is summarized in Table 3.4. All subjects gave their written informed consent to participate in this study.

TABLE 3.4: Clinical and demographic information.

Sub	*Etiology of injury*	*Age*	*Months since injury*	*ASIA*	*NLI*	*Gende r*	*Dom. arm*	*Stim . arm*
S1	Infectious	71	4	C	C5	Male	R	L
S2	Traumatic	38	10	C	C5	Male	R	L
S3	Traumatic	36	7	B	C6/C7	Male	R	R
S4	Postsurgical	55	4	D	C5	Male	R(*)	R

ASIA: American Spinal Cord Injury Classification
NLI: Neurological Level of Injury
Stim. arm: arm which performed the BMI + FES sessions
Dom. Arm: dominant arm
R: Right
L: Left

(*)Arm dominance of S4 changed after the injury, from right to left

3.4) Description of the protocol of the feasibility study with patients

We carried out a feasibility study with 4 patients with iSCI (ASIA B, C or D [18]), who performed 5 sessions with the BMI + FES + virtual reality feedback device. The aim is to analyze the feasibility and usability of the device as a tool for neurorehabilitation and assess the immediate effects on the patients after using the system. To this end, the intervention was applied to one of the patient's arms, from now on referred as "stimulated arm", whereas the other will be referred to as "non-stimulated arm".

The patients used their motion intention to trigger a grasping movement with FES, while simultaneously receiving a visual feedback of a virtual hand closing. Initial and final clinical assessments were performed, as well as a usability test and an exertion test that the 4 patients answered after the study.

The experiments were conducted in accordance with the Helsinki Declaration. The experimental protocol consisted of 5 sessions, with an approximate duration of one hour each. A clinician performed a visual evaluation of the response of the patient's hands to FES, in order to select the most appropriate hand for the intervention, following the inclusion criteria (2) and (4) previously defined. In case that both hands met both inclusion criteria, the most affected hand was selected.

Fig. 3.1 b shows a patient during a therapy session. Each session was performed in a different day, completing the 5 sessions within a maximum time interval of 10 days. During the experimental sessions, the patients were seated on their wheelchairs, facing a computer screen, and with the FES electrodes attached on one of their arms. The sessions consisted of screening blocks and feedback blocks. The screening blocks were performed to acquire data for the BMI calibration, whereas the feedback blocks entailed a closed-loop intervention that associated the brain patterns of motor attempt with the simultaneous activation of FES and virtual reality feedback.

During the screening blocks, the words "Rest" and "Movement" were indicated alternatively to the patients through the computer screen. They were asked to rest or to perform MA of the hand selected for the therapy, following the cues displayed on the screen. The "Rest" period lasted randomly between 4 and 7 seconds, and the "Movement" interval lasted 3 seconds. These blocks consisted of 20 trials without any feedback.

For the closed-loop feedback blocks, the patients were also placed in front of a screen where the virtual hand was displayed, and the FES electrodes were placed on the arm selected by the clinician. The feedback blocks consisted of 20 repetitions each, in which the subjects performed MA, receiving 2 seconds of FES and virtual reality feedback when the system correctly detected the attempt. Each repetition started with 10 seconds of rest, followed by 3 seconds of MA. If the BMI detected the motion intention in the MA interval, the patient was stimulated, otherwise, the next repetition started.

On the first session, the patients were asked to perform 4 screening blocks (therefore a total of 80 trials to train the classifier) and 2 feedback blocks (40 trials with the closed-loop system), whereas on the remaining 4 sessions they were asked to perform 2 screening blocks (40 trials) and 4 feedback blocks (80 trials).

3.5) Outcome measures

3.5.1) Clinical scales

Each patient performed an initial (1 day before the intervention) and a final (1 day after the intervention) evaluation that consisted of the application of the clinical scales Spinal Cord Independence Measure (SCIM III) [103] and the GRASSP (Graded and Redefined Assessment of Strength, Sensibility and Prehension) [60]. SCIM III is a scale specifically designed to measure independence of SCI patients. It consists of 3 sub-items: self-care, mobility, and respiration and sphincter management. Since our intervention is focused exclusively on the grasping movement, improvements in mobility and respiration and sphincter management are out of the scope of this work and, therefore, the scores obtained in these sub-items are not shown.

GRASSP scale assesses 3 different hand function domains: strength, sensibility, and prehension (quantitatively and qualitatively). With the aim of evaluating the motor effects of the BMI + FES therapy, we used the strength, prehension-qualitative and prehension-quantitative sub-items, which are directly related to motor function, whereas the sensation sub-item was used as an indicator of the usability of the system, to find out any side-effect derived of the FES. GRASSP strength sub-item evaluates 10 upper limb muscles (graded between 0 and 5) separately for left and right side, giving a maximum score of 50 for each side.

3.5.2) Usability assessment

All patients were asked after the last session to fill in a usability and satisfaction survey, to evaluate the possibilities of incorporating the integrated system in a clinical environment. The questions that comprised this test were adapted and translated from a previous questionnaire [104]. The possible answers followed the Likert scale: 1 ("I strongly agree with the sentence"), 2 ("I agree"), 3 ("Neutral"), 4 ("I disagree"), and 5 ("I strongly disagree"). The exertion was evaluated through the Borg Scale, whose values range from 6 ("very, very light") to 20 ("very, very hard") [105].

3.5.3) BMI accuracy

BMI accuracy has been evaluated as the percentage of trials correctly decoded by the system for every patient. Moreover, we have extracted the amplitude of two neurophysiological phenomena, which have been demonstrated to correlate with the movement intention; namely the event-related desynchronization (ERD) and the motor related cortical potentials (MRCP).

4. RESULTS

4.1) Usability and immediate effects

The results of the usability and satisfaction tests are presented in Table 3.5. Patients generally agreed with the statements regarding satisfaction and the will to continue using the system (e.g., questions 1, 2, or 9), and disagreed with the questions implying difficulties or discomfort (e.g., questions 5 and 6). In terms of exertion, according to the Borg Scale, subject S1 rated the degree of exhaustion during the use of the system with a 9 ("very light"), S2 with a 13 ("somewhat hard"), S3 with an 11 ("fairly light") and S4 with a 6 ("very, very light").

TABLE 3.5: Usability and satisfaction scores for all patients.

Question	***S1***	***S2***	***S3***	***S4***
1. I would like to use these applications in therapy	1	1	1	1
2. The application was more engaging than the exercises I have done before	3	2	1	1
3. The application was more strenuous than the therapy I have done before	3	3	1	5
4. I could see myself using this kind of applications in the future	1	2	1	2
5. It was hard to understand the directions for using the application	5	5	1	4
6. I felt frustrated while using the application	5	4	5	5
7. I was motivated to keep using the application.	2	1	2	1
8. It was easy to understand how to use the controller to use the application	1	2	1	2
9. I feel as though I would benefit from using this kind of applications in therapy	1	1	1	1

1 ("I strongly agree with the sentence"), 2 ("I agree"), 3 ("Neutral"), 4 ("I disagree") and 5 ("I strongly disagree").

No adverse effects were observed in any of the patients, and, in general, there were higher improvements in their quantitative prehension in the stimulated arm compared with the non-stimulated arm, as it can be extracted from Table 3.6. In one of them (S3), there was a 1-point increase in the stimulated arm in contrast to a 2-point decrease in the non-stimulated arm. Regarding prehension quality, 2 patients (S1 and S4) showed higher increases in the stimulated arm than in the non-stimulated arm, whereas the other 2 (S2 and S3) did not undergo any change in any of the arms.

As explained above, results of sensation (shown in Table 3.7) are not interpreted as an expected outcome of the experimental therapy, but as a measure of any side-effect of the electrical stimulation. 2 patients (S2 and S4) showed a decrease in dorsal sensation according to the GRASSP scale in the stimulated arm in contrast with an increase in the non-stimulated arm; whereas S3 showed approximately the same score pre/post intervention in both arms, and S1 showed a decrease in the non-stimulated-arm in contrast

TABLE 3.6: Pre-post comparison of GRASSP prehension and strength scores in the stimulated and the non-stimulated arm.

Sub	*Arm*	*Strength (max 50) PRE/POST*	*Prehension-Qualitative (max 12) PRE/POST*	*Prehension-Quantitative (max 30) PRE/POST*
S1	**Stim.**	33 / 30	6 / 9	10 / 15
	Non-stim	33 / 31	9 / 9	14 / 16
S2	**Stim.**	19 / 20	4 / 3	10 / 12
	Non-stim	17 / 20	4 / 3	6 / 7
S3	**Stim.**	18 / 17	2 / 2	13 / 14
	Non-stim	15 / 17	1 / 1	13 / 11
S4	**Stim.**	30 / 31	7 / 8	20 / 24
	Non-stim	43 / 45	11 / 10	28 / 28

Stim: Stimulated arm
Non-stim: Non-stimulated arm
PRE/POST: before/after intervention

with a small change in the stimulated-arm. Regarding palmar sensation, changes were very similar between both arms. Therefore, there is not a general pattern of changes in dorsal and palmar sensation, since they are very small and different for each patient, so they can be attributed to the progress of the injury. Hence, there is no observable side-effect of FES. In terms of self-care ability (measured by SCIM III sub-item), only 1 patient improved his score (S3), another one got worse (S4) and the other 2 patients (S1 and S2) obtained the same scores before and after the intervention, as it can be seen in Table 3.8. SCIM-III Total score (range between 0 and 100) is reported only with the aim of offering an overview of the functional status of the patients before and after the intervention.

4.2) BMI accuracy

In total, 360 test trials were recorded for each patient (40 on session 1, and 80 on each of the subsequent sessions). The BMI correctly decoded 79.13 ± 13.80% of the trials for all subjects and sessions. Fig. 3.9 shows the percentage of decoded trials for each subject and session, as well as the average of all of them.

TABLE 3.7: Pre-post comparison of GRASSP sensation scores in the stimulated and the non-stimulated arm.

Sub	*Arm*	*Sensation-Dorsal (max 12) PRE/POST*	*Sensation-Palmar (max 12) PRE/POST*
S1	**Stim.**	6 / 7	9 / 8
	Non-stim	11 / 6	11 / 10
S2	**Stim.**	8 / 6	5 / 4
	Non-stim	3 / 6	2 / 0
S3	**Stim.**	7 / 7	8 / 8
	Non-stim	7 / 8	8 / 7
S4	**Stim.**	12 / 11	10 / 11
	Non-stim	9 / 11	10 / 12

Stim: Stimulated arm
Non-stim: Non-stimulated arm
PRE/POST: before/after intervention

TABLE 3.8: Independence scores obtained by all subjects (SCIM III scale).

Sub	*SCIM III Total score (max. 100) PRE/POST*	*SCIM III Self-care (max. 20) sub-item PRE/POST*
S1	19 / 26	3 / 3
S2	27 / 28	4 / 4
S3	29 / 34	3 / 6
S4	28 / 42	8 / 5

PRE/POST: before/after intervention
SCIM III: Spinal Cord Independence Measure III

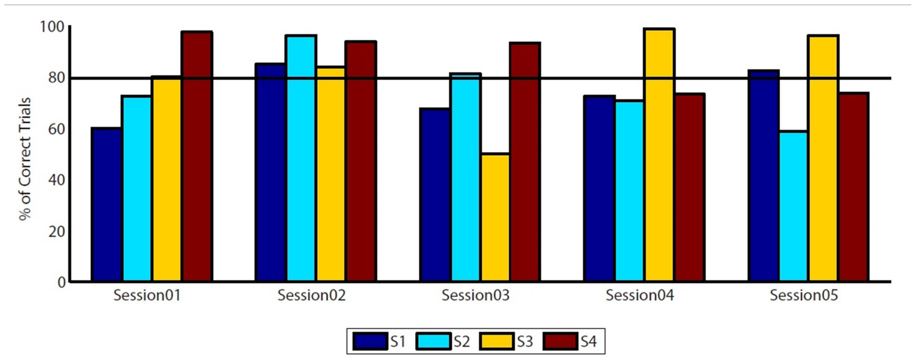


Fig 3.9 Percentage of correctly decoded trials for each subject and session. Each bar color corresponds to one subject. Black line represents the average for all subjects and sessions

The average delays obtained by patients are shown in the figure 3.10. The average of the 4 subjects was 1.4 s between the appearance of the cue and the response of the system.

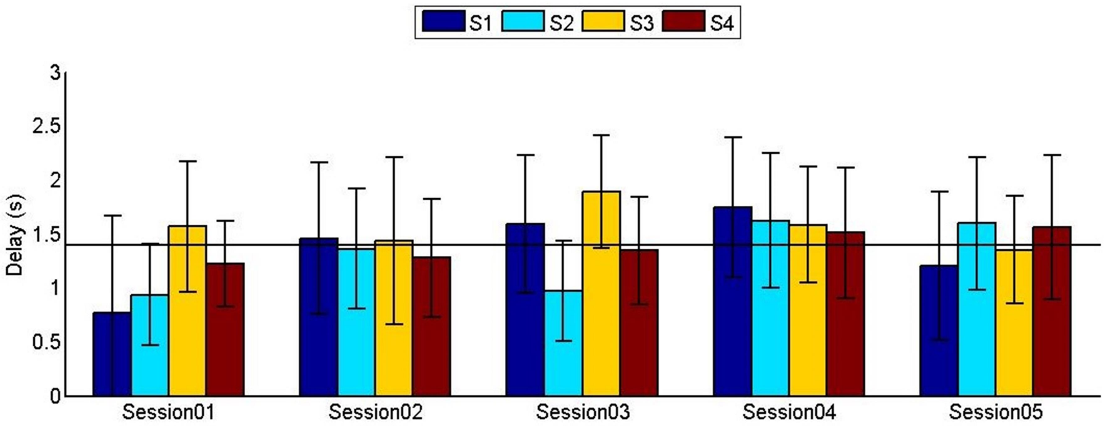


Fig 3.10 Average and standard deviation of the delay between cue and response of the system. Each bar color corresponds to one subject. Black line represents the average for all subjects and sessions

As we performed a recalibration before each session, we wanted to measure what was the influence of such recalibration in the decoding performance. Hence, we simulated offline the performance of the decoder as if it had been trained with the data recorded only during the first session (i.e., if no recalibration had been performed in every session). On average, such decoder decoded correctly 58.5 ± 32.48% of the trials. A Wilcoxon paired test comparing the percentage of correctly decoded trials for each subject and session revealed that recalibrating the classifier before each session provided significantly higher decoding results ($p < 0.05$). Furthermore, the performance of this recalibration scheme versus other methods has been evaluated in a parallel work [106].

4.3) Neurophysiological analysis

Fig. 3.11 displays the neural correlates of the motor intention, corresponding to the first screening session, averaged for all patients. Notice that, as 2 patients performed the therapy with their left hand (S1 and S2) and 2 patients with their right hand (S3 and S4), for this offline analysis we swapped the lateralized channels of patients S1 and S2, so that we averaged their signals simulating that all of them performed the intervention on their right hand. Bilateral ERD appeared on α and β frequency bands, especially in channels C3 and C4. Conversely, MRCP appeared more lateralized towards the left hemisphere, showing maximum amplitude in channels C3 and C1.

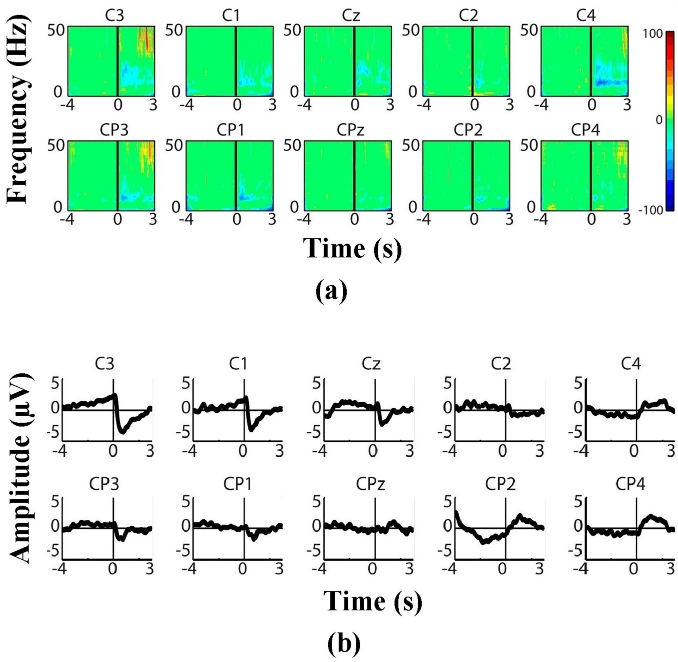


Fig 3.11 (a) Significant ERD in ten channels over the motor cortex (*x* axis corresponds to the time interval [-4, 3], *y* axis represents the frequency range [1-50] Hz). (b) Average MRCPs for all patients in ten channels over the motor cortex (*x* axis corresponds to the time interval [-4, 3], *y* axis represents the MCRP amplitude)

4.4) EEG features

The classifier used an automatic procedure to extract the features for each subject. Therefore, a post-hoc analysis was carried out to visualize those selected features, which can be seen in Figure 3.12. It can be observed that more frequency features (ERD) were selected than temporal ones (MRCP) for all patients. ERD features are more consistently detected in central and centroparietal electrodes. Channel C4 was the most frequently

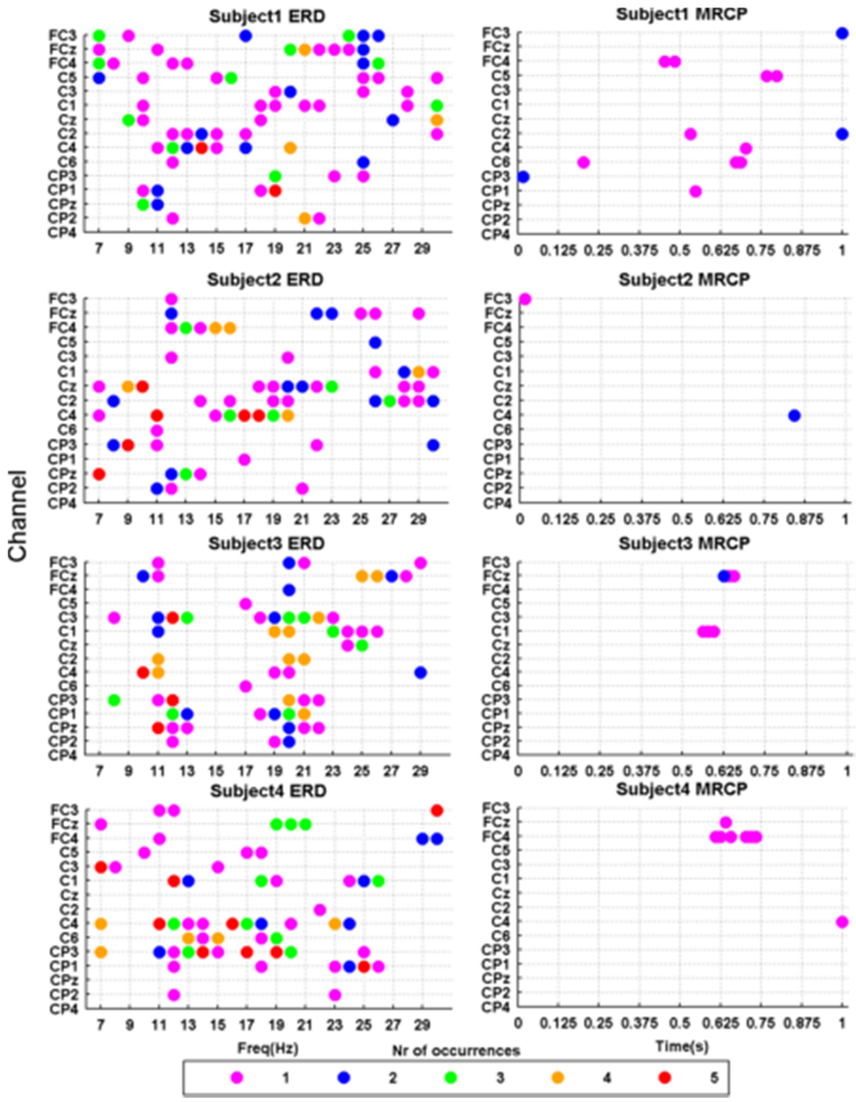


Fig 3.12 EEG features selected by the SDA classifier for each subject. The left part shows the ERD features as channel-frequency pairs, whereas the right part shows the MRCP features as channel-time pairs. The number of occurrences is the number of sessions in which each feature has been selected

selected for subjects 1 and 2, C3 for subject 3 and CP3 for subject 4, which is consistent with the MA that they performed, since subjects 1 and 2 carried out left hand MA and subjects 3 and 4 right hand MA.

5. DISCUSSION

This work proposed a system combining BMI and FES therapy complemented with virtual reality feedback for neurorehabilitation of patients with iSCI. The system was validated in 4 patients, showing very positive results in terms of usability and exertion, promising outcomes in clinical scales, and good levels of accuracy.

All patients reported that they would like to use this kind of application in therapy. They also rated that the system was easy to use. In terms of motivation, the answers to the questions 6 and 7 of the questionnaire revealed that patients did not feel frustrated while using the system, and they were quite motivated. We believe that two factors played an important role in these results: the combined feedback provided by the therapy and the high accuracy obtained by all patients in all sessions. From the first session, the patients obtained acceptable values of accuracy. Furthermore, the patients did not show any harmful effect neither during nor after the therapy. In terms of exertion, three out of the four patients rated the effort of using the system as light, and only one of them rated it as "somewhat hard".

One of the main reasons of the good acceptance of the system by the users is probably its stable and predictive behavior to trigger the feedback. In order to achieve this, we had to carry out a short recalibration of the system at the beginning of each session (less than 10 minutes of recording and data processing) that significantly improved the decoding results. This is crucial to guarantee that the patient receives a sufficient dose of brain-triggered electrical stimulation during the intervention sessions and to make him feel that he controls the system. Indeed, all patients reported to have this feeling of commanding the movements of their affected arm with their own brain. This kind of functional coupling is an important factor to promote neural plasticity [107].

We believe that another important factor of the high motivation of the patients was that the setup time was less than 15 minutes, thus maximizing the available time for therapy. Other authors have emphasized that this is a key aspect to translate BMI applications to the routine of rehabilitation [108].

All patients showed higher improvements of their quantitative prehension in the stimulated arm compared with the non-stimulated arm. This preliminary result should be interpreted with caution, due to the small sample of patients, but it is considered as positive, since the system was designed with this aim. Half of the patients also improved their quantitative prehension.

Another important observation is that the system is also appropriate for patients without any residual motor function in the affected limb (such as in severe tetraplegia or hemiplegia) and, therefore, cannot use systems based on muscular activity. Patient S3, with ASIA B, was unable to volitionally move his fingers, but was able when using the system to perform a complete hand grasping. Although this ability was not translated into functional recovery during the study, it is a starting point to involve these patients in future studies with these technologies.

The therapeutic approach described in this study provides somatosensory and virtual reality feedback during the execution of repetitive tasks, supporting motor relearning [109]. Although FES has shown efficacy itself, due to the muscle contraction elicited by orthodromic activations [110], we believe that combining FES with BMI can provide even better results. The BMI allows synchronizing the antidromic impulses induced by FES with the voluntary motor commands decoded in the EEG, which may support the rewiring of the neurons by coincident voluntary motor commands through Hebb-type modifiable synapses [111]. Furthermore, previous studies with stroke patients have shown that combination of BMI and FES induces higher improvements than FES alone in motor function, electromyographic activations, and brain plasticity [107]. Since iSCI patients still maintain certain neuronal pathways, combination of BMI and FES may also be beneficial for their rehabilitation, as it is in stroke population. The main weakness of the electrical stimulation as feedback is the high variability in muscle responses that patients experiment even for constant FES values [16]. To overcome that limitation, we propose the use of the virtual reality feedback, designed to match closely the real task that the subjects had to carry out, namely closing the hand. This feedback was well tolerated by the subjects, since they perceived that the movement of the virtual hand was synchronized with their volitional commands. For future studies, the use of virtual environments in BMI settings may enable to perform more complex tasks, such as grasping different objects, therefore enhancing the motivational component of the therapy. Hence, we consider that the combination of BMI+ FES + Virtual reality feedback may take advantage of the benefits of each and every one of them, enhancing the rehabilitation outcome.

Two types of neural correlates were used to control the BMI: the ERD and MRCPs. They were present in the four subjects and did not change significantly across sessions, which allowed for fast recalibration between sessions. Several works have shown that both types of correlates are weaker for complete SCI patients than for healthy subjects during motor tasks [87][112]. We are only aware of two studies on iSCI patients that also reported the presence of both correlates with similar activations to those of healthy subjects [28][113]. Although our findings support previous results, further research on a larger population is necessary to characterize these brain patterns for iSCI patients and assess the impact on BMI performances. Also, it is still an open question whether it is better to ask patients to attempt to move or to imagine movements to promote recovery. Despite both of them can be decoded with a BMI [114], we asked the patients to attempt to move so that the actual motor command would reach as far as possible into the spinal circuits, given that motor imagery requires suppression of movement [107].

Finally, as limitations of the work, we want to remark that, because of the nature of this feasibility study, the number of participants is small, so further research with a larger number of subjects and a control group will be necessary to confirm these results. Due to the novelty of this kind of therapeutic applications of the BMI technology, we consider essential to gather as much information as possible before envisaging a clinical study with a larger sample.

6. CONCLUSIONS AND MAIN CONTRIBUTIONS

The conclusions and main contributions of this section of the thesis are:

1. The novelty of the integration of BMI, FES and virtual reality as therapy for SCI patients, allowing the patients to control both systems by themselves, without external assistance

2. The system showed high levels of accuracy throughout the different sessions (79.13 % on average).

3. The accuracy of the system in detecting motion intention remained stable throughout the different sessions, so we can conclude that the designed algorithms are sufficiently robust.

4. Sparse discriminant analysis, a machine learning technique to reduce dimensionality and classify data, has been successfully applied to the BMI domain.

5. An algorithm combining temporal features (MRCP) and frequency features (ERD) has shown to be effective for SCI patients to detect motion attempt of the upper limbs.

6. The algorithms developed in this work also allow to analyze the most relevant neurophysiological features for each patient, which is very important to provide a system that could serve to perform therapy and, also, to assess patients.

7. The delay between motion intention and response achieved by the system is sufficiently short to provide the patients the sensation of immediate control of both FES and VR, which is essential for the therapy success.

8. The therapy device has been safely tested by patients, without observing any adverse effects in any of them.

9. In terms of usability and exertion, all patients showed their satisfaction after the use of the application.

10. Promising clinical outcomes have been obtained by 4 patients with iSCI after performing 5 therapy sessions with the system, as small improvements of their quantitative prehension in the stimulated arm compared with the non-stimulated arm. Therefore, we conclude that the design of the system correctly accomplished the desired aims.

11. The results of this work support the feasibility of a BMI + FES + virtual reality feedback to be considered as a therapeutic tool for upper limb rehabilitation.

CHAPTER 4: EEG DERIVED METRICS TO ASSESS NEUROPLASTICITY CHANGES IN NEURORREHABILITATION

1. INTRODUCTION

Some studies have suggested [11], [12], [107] that the synchronization between descending information from the brain (throughout motor intention) and afferent information from an external stimulus that BMIs allow, can facilitate the reconnection of damaged neurons based on Hebbian learning theory [5]. However, there is insufficient evidence to conclude that these therapies really promote neuroplasticity. Some studies have shown, by using functional magnetic resonance imaging, that there are effective changes in the intensity and in the activated areas when motion imagination is performed after the completion of a number of BCI sessions [82], [115], [116]. However, these changes are not always directly related to an improvement in the patient's functionality, since characterizing the brain as a set of disjoint areas dismisses the complex and timed interactions that take place to perform any action [117]. Accordingly, it is necessary to find other metrics that reflect more naturally the flow of information within the brain and therefore could be more directly related to the regenerative processes of the nervous system, based on the idea that the brain tends to organize its connections as effectively as possible. Since the brain works as a complex network of neural assemblies, it is essential to study the interactions between the different areas. One of the most popular methods to assess this interaction is to measure brain connectivity [33]. Moreover, it has been suggested that a connectivity-based study of the brain could be more related to pathological changes than the traditional approach of measuring the activation changes of disjoint areas [118].

Although fMRI has been broadly used to study interactions between brain áreas, EEG presents several advantages that make this technology an ideal candidate to study the brain as a dynamic system [34], specially its temporal resolution [33]. Other characteristics make EEG highly useful in the context of rehabilitation technologies, such as its portability, non-invasiveness and relative low cost. Therefore, it is relevant to find EEG-based metrics in order to assess neuroplasticity in patients at the same time that they are performing a therapy. However, in order to find useful metrics, it is necessary to overcome some limitations of EEG technology, such as the fact that EEG poorly measures neural activity that occurs below the upper layers of the brain (the cortex) making impossible to measure the interaction between lower layers. Moreover, EEG presents a low spatial resolution. Due to this reason, the aim of this work is to determine whether the information provided by EEG could be sufficient to obtain clinically relevant information.

2. STATE OF THE ART

Firstly, it is necessary to review the different methods that have been used to determine connectivity from EEG recordings, considering their advantages and limitations. It is important to begin distinguishing between 2 terms: functional connectivity (FC) and effective connectivity (EC). The first term refers to symmetric and undirected correlations between the activity of cortical sources, whereas the second refers to directed or causal dependencies [29]. The earliest studies calculated FC through linear correlations and coherences between EEG signals from the scalp [30], [31]. These techniques present a serious risk of misidentification in systems with correlated noise, strong autocorrelation, such is the case of brain signals [32]. Despite this, both are among the most used tools to assess connectivity in the field of neuroscience [33]. Some examples of EC techniques are dynamic causal modeling (DCM), directed transfer function (DTF), structural equation modeling (SEM), transfer entropy (TE) and Granger causality (GC) method. A division of these techniques in 2 groups (model-based or data-driven) will be given in the following lines, together with a brief description of each one:

- Model-based effective connectivity: these techniques use neurobiologically-inspired theoretical models. DCM and SEM lie within this group.
    - DCM: the key idea of this technique is that a dynamic system can be modeled by a network of discrete but interacting neuronal sources [33].
    - SEM: this technique approaches neural data by considering the covariance structure. Parameters are estimated by minimizing the difference between

the observed covariances and these implied by a structural or path model [119].

- Data-driven effective connectivity: they do not assume any underlying model or previous knowledge about underlying spatial or temporal relationships [33]. GC, DTF and PDC lie within this group.
    - GC: Granger causality is based on the idea that if a signal can be predicted from previous information of a second signal better than from its own past information, then it is said that the second signal is Granger causal to the first [33]. According to Nolte *et al.* this method may be very sensitive to noise when there are individual noisy channels, since spurious connectivity patterns would be obtained [34].
    - DTF: Directed Transfer Function measures the influence of element j to element i with respect to the influence of all the other elements on i, similarly to Granger causality. According to Hamedi *et al.,* it is quite robust against noise and volume conduction (VC), a phenomenon that will be further explained [120]. However, since this method can be regarded as a version of GC [121], Nolte *et al.,* claimed that may elicit spurious connectivity patterns [34].
    - PDC: Partial Directed Coherence can be considered a spectral version of GC [122]. It quantifies the relationship between 2 out of n signals, while avoiding volume conduction (the most typical handicap of traditional coherence) by accounting the interactions from the other n-2 signals [33].

With respect to functional connectivity (FC), a division between lineal, non-linear and information-based techniques can be established.

- Linear connectivity: cross-correlation, magnitude squared coherence (MSC), Wavelet coherence (WC) and imaginary part of coherence (IC) lie within this group:
    - Cross-correlation: it was one of the first techniques used to measure connectivity, early in the 1950s [30], [31], identifying functionally connected areas with highly correlated signals.

- MSC or simply coherence: it is computed as the cross-spectral density function (which is equal to the squared Fast Fourier Transform) normalized by their individual autospectral density functions. It allows to measure spatial correlations in different frequency bands [123]. Due to the finite amount of data available in EEG recordings, spectrum is usually estimated (known as periodogram) using smoothing techniques such as Welch method [124]. MSC gives information in terms of power and phase changes of any of the 2 signals under study; however, it does not give the actual relationship but the stability of this relationship [33]. MSC is affected by the window length and overlap chosen to calculate the spectral density.
- Wavelet Coherence (WC): it is an alternate method to compute coherence. It requires previous information about frequency and time ranges of coupling. It is particularly useful to calculate time-varying coherence, since it uses a shorter window for higher frequencies and a longer window for lower frequencies, instead of the constant length of the window used to calculate the spectrum in MSC technique. WC presents the enhancement that it allows to obtain a probability distribution of the calculated coherence. This can be interesting for clinical studies, since it gives the significant changes of WC with respect to a population average, for example [33]. Additionally, if the windows used to calculate the coherence are short enough, stationarity can be assumed.
- Imaginary part of coherency (IC): this is a particularization of the coherence, developed by Nolte *et al.*, which is based on the assumption that the imaginary part of the coherency is insensitive to volume conduction [34].The rationale for this is that a scalp potential has no time-lag with respect to its source [125] and imaginary part of coherency is only sensitive to processes that are time-lagged to each other, so it cannot be affected by potentials caused by the same source.

- Non-linear connectivity: these metrics are not designed to overcome linear methods, but to account for non-linear phenomena that are fundamental in the neural system, such as the regulation of the voltage-gated ion channels, which depends on a steep non-linear relationship between the membrane potential and the current flow [33]. Non-linear connectivity techniques are based on the measurement of synchronization. There are mainly 4 different methods to calculate synchronization: phase locking value (PLV), generalized synchronization (GS), phase lag index (PLI) and weighted phase lag index (WPLI):

- PLV: it is computed from the Hilbert Transform, which calculates instantaneous phase. This method assumes that two dynamic systems may have their phases synchronized even if their amplitudes are zero correlated [126]. It does not require stationarity of the signals. According to Niso *et al.* this method is not robust against volume conduction [127].
- GS: this strategy is based on the idea that neurons are highly non-linear systems, which sometimes exhibit chaotic behavior. Therefore, according to this premise, it might be useful to use non-linear measures in neurophysiology analysis [128].
- PLI: it is less sensitive to common sources, since it is based in the idea that a consistent phase lag between two time series cannot be explained by VC from a single common source [129].
- WPLI: it takes into account not only the phase, but also the amplitude of the imaginary component of the cross-spectrum. In this way, relative phases corresponding to small amplitudes of the imaginary cross-spectrum have a small impact in the index [130].

- Information-based connectivity: these techniques are able to detect both linear and nonlinear interactions. Cross-mutual information (CMI), minimum description length (MDL) and transfer entropy (TE) lie within this category:
  - CMI: it quantifies the mutual dependence of two signals by measuring the quantity of information one signal gains by measuring the other. It is given in function of the delay between the two signals [33]. The main strength of this technique is that it is able to detect high-order correlations [120].
  - MDL: the key idea of this technique is that the best model for representing a signal is the one with the shortest possible code length. Therefore, the

savings in code of one signal by knowing the other are a measure of the dependence between them [131].

- TE: it incorporates directional and dynamical information because it is inherently asymmetric and based on transition probabilities [132].

One of the main difficulties to overcome when measuring connectivity from EEG recordings is the volume conduction. This process originates from the fact that surface EEG recordings do not offer direct information from the neural sources, but instead they measure a superposition of electrical activity from different sources. Moreover, this activity is distorted by the skull, scalp and other conductive tissues. These effects together are known as volume conduction [120]. This process may produce spurious correlations and therefore misinterpretations of spatial analysis of the EEG [133]. There are several approaches to address this problem,, such as designing connectivity metrics which eliminate instantaneous effects[34], [134]–[136]. Another interesting metric that was developed with the same aim was phase lag index (PLI), which is less sensitive to common sources, since it is based on the idea that a consistent phase lag between two time series cannot be explained by VC from a single common source, and therefore it is able to render true interactions between brain areas [129]. However, it presents a limitation due to its discontinuity; since small perturbations may turn phase lags into leads and vice versa. This limitation has been overcome by developing a weighted version of PLI (WPLI), as we have already mentioned.

According to Makeig et al in 2012, effective connectivity techniques better reflect the underlying cortical activity and therefore, their potential in BCI field is higher [117].

There is not an ideal connectivity metric; their suitability depends on the particular phenomena or population under study. Sensitivity to more aspects of the neural dynamics may be a desirable property but, at the same, it may turn the metric less robust[34]. With respect to the distinction between linear and nonlinear metrics, it is questionable that non-linear methods are superior to the linear ones, unless the non-linearity is the specific target of the study [34].

In addition to the connectivity metrics already described, graph theory offer some parameters that may help to better quantify EEG networks, and therefore, provide clinically relevant information. Graph theoretical approaches applied to EEG define the electrodes as vertices and the connections between them as edges. They are usually given in combination with functional connectivity metrics, since the latest provide the information regarding the connections between electrodes that will be used to build the network.

There are two groups of theoretical graph metrics: regional and global. The first refers to the properties of individual nodes and their influence in the network, whereas global metrics describe parameters of the whole network. In order to choose the most appropriate one, it is important to consider that global network metrics have shown to be less reliable than regional ones in a test-retest experiment, in which regional and global metrics were evaluated in functional magnetic resonance images of the same subjects with 5 months of difference [137]. This experiment revealed that regional metrics were more robust against noise than global ones.

Previous studies have gathered information about neuroplasticity-derived changes from EEG recordings. De Vico et al. analyzed functional connectivity by comparing 5 healthy and 5 SCI subjects, and applied graph theory metrics [35]. They calculated functional connectivity (FC) by using Direct Transfer Function (DTF). They found that, for 3 frequency bands (theta 4-7 Hz, alpha 8-12 Hz and beta 13-29 Hz), local efficiency was higher in SCI subjects than in healthy ones, suggesting higher fault tolerance and a larger level of internal organization, as a compensatory mechanism in response to the injury. Youssofzadeh et al. found negative correlation between frontoparietal FC (calculated by Partial Granger Causality) and kinematic error (difference between the ideal and the actual trajectory) in healthy subjects while walking with the aid of an exoskeleton [138], suggesting that this FC could serve as a marker of motor learning and adaptation.

It is of special interest in the field of rehabilitation technologies to find assessment metrics that correlate with clinical improvements, and, therefore can be useful for the clinicians to quantify and objectively study patient's evolution. There have been several studies that have found correlation between motor recovery and brain activity in SCI patients. One of these studies, carried out by Jurkiewicz *et al*, found that motor cortex activation measured with fMRI at different time points along the first year after injury was significantly correlated with ASIA motor score [139]. They also found that the activity in sensorimotor areas, such as Supplementary Motor Area (SMA) increased in SCI subjects with respect to healthy ones and progressively decreased with the recovery. Other study by Hou *et al.* analyzed by fMRI the connectivity patterns of SCI subjects in comparison with healthy controls. They obtained interesting findings, such as increased intra-hemispheric and decreased inter-hemispheric FC in SCI patients compared to healthy controls. They found that FC between left primary sensorimotor cortex and left cerebellum was increased in SCI patients, and this FC was negatively correlated with ASIA motor score. They also found that FC between right primary sensorimotor cortex and right SMA was increased in SCI patients and it was also negatively correlated with ASIA motor score [140]. The latest finding is of special interest for our work, since both areas are easily recordable by EEG. They speculated that the inter-hemispheric decreased FC implies the loss of information transfer efficiency between both hemispheres, due to the interruption of the efferent and afferent pathways, whereas the increased intra-hemispheric FC reflects axon sprouting generating new pathways that may compensate the impaired pathways [140]. This increased intra-hemispheric FC was negatively correlated with ASIA motor score; hence it remained unclear whether this regenerative mechanism is leading to functional recovery. However, a later study from the same author showed that recovery rate in SCI subjects was positively correlated with FC between right primary motor cortex (M1) and right SMA, and also with FC between right M1 and right premotor cortex (PMC)[141]. The rationale they suggest to explain this phenomenon is that one of the main recovery mechanisms after an insult to the nervous system is the recruitment of new motor areas to compensate the reduced capacity of the primary motor cortex to produce a sufficient motor output, which is in line with the findings of other studies on patients with stroke [142], [143], as well as with other study that showed that the PMC was one of the main contributors to the motor recovery of SCI patients 3-4 months after injury [144]. Despite of the importance of these studies, all of them have been performed using fMRI to calculate FC, more specifically, in the case of Hou *et al.*, they use frequencies between 0.01 Hz and 0.08 Hz, of BOLD signals, a phenomenon known as Low Frequency Fluctuations. Therefore, it remains unclear whether FC obtained from EEG signals could be correlated with clinical scores in

SCI patients, which is of special interest for portable neurorehabilitation technologies as the one presented in this work.

There are a couple of studies that have found correlation between FC and motor outcomes reached after completion of a BCI therapy, but none of them in SCI patients. Varkuti *et al.* found in patients with stroke, after performing a therapy with an upper limb robot controlled by a BCI, positive correlation between Fugl-Meyer Scale and changes in FC between Inferior Parietal Lobe (IPL) and the SMA and between the Anterior Cingulate Cortex (ACC) and the SMA [145]. In another study, Young *et al.* found in stroke patients after performing a BCI-mediated neurofeedback therapy some correlations between clinical scale changes and FC changes between different areas, specially between the thalamus and the motor cortex and between the thalamus and the cerebellum [37]. However, some of these correlations were positive and some others were negative, thus suggesting that FC changes due to brain reorganization can be also maladaptive, which is in line with other studies [38]. Therefore, there is a need of further investigating about which of these FC changes are directly related with positive neuroplasticity, especially in SCI subjects since, to the best of our knowledge, there are no studies on changes in FC after a BCI-therapy in subjects suffering such injury.

3. METHODS

We are interested in developing FC metrics that could be applied in a BMI therapy. These metrics should therefore meet the following requirements:

- They need to show information that could be clinically relevant. This is probably the most subjective point, since the clinical relevance depends on what is considered as such by medical experts. In the case of this study, as we have done in Chapter 2 with the virtual reality study, we are going to rely on clinical assessments. Therefore, we look for metrics that could be correlated or, at least, that show similar trends than the scores of the clinical scales.

- We focus on the real application of BMI systems, in such a way that the defined metrics could be potentially applied in a low-cost BMI (namely, with a small number of electrodes).
- The metrics should have a neurophysiological rationale. With this aim, an analysis of the state of the art was performed, in order to identify the brain interactions that could reflect progress in the SCI patients' rehabilitation. Thus, the metrics defined here are tailored to the characteristics of patients with SCI, although its application in other populations such as stroke patients should not be dismissed, according to the existing similarities between neurological injuries.

Keeping these requirements in mind, two metrics of FC have been applied to EEG data in order to analyze their performance in a BMI context: imaginary part of coherency (IC) and weighted version of phase-lag index (WPLI). Both of them are less sensitive to volume conduction than the other metrics, therefore we believe that they could be adequate in a BMI environment. IC is a linear metric, whereas WPLI is non-linear, hence comparing the brain interactions that both metrics are able to unwrap, will allow us to determine if EEG linearity can be assumed or not. After studying which brain interactions are more directly related to clinical status of the patients, we will develop a new metric comprising this information, to offer a global synchrony metric (GSYM) that could be used as a method of assessment brain changes during neurorrehabilitation therapies. This metric pretends to offer a synthesis of brain activity changes from different areas.

The EEG recordings used to compute the neuroplasticity metrics come from the BMI+FES+VR experiments already described in Chapter 3. In them, 4 subjects performed 5 sessions controlling a FES and a VR feedback directly from their own intention, by MA of the upper limbs. There were screening sessions (used to gather data in order to train the classifier) and interactive sessions (with FES and VR feedback). We analyzed EEG recordings from the screening sessions after the cue appearance (therefore, since t=0 s to t=3 s), because we are interested in studying brain activity related with motor intention. In order to find correlations between clinical assessments and neuroplasticity metrics, we considered the first and the last session for each patient.

Before applying the different FC techniques, there are several pre-processing steps that must be applied in order to obtain appropriate electrophysiological information. These steps are summarized in the following section:

3.1 Pre-processing of the EEG signals

- Choice of the EEG reference: our study has been conducted with a common referenced montage (ear reference). However, these conventional montages can be affected by confounding activity. Therefore, there are some methods to re-reference the data offline, in order to minimize its harmful effects [146]. One of them is Common Average Reference (CAR), but it is less effective in low density EEG recordings, such as the case of our study. Other methods are infinite reference, that tries to estimate a time-varying constant that is removed from the recorded data [147] and surface Laplacian (SL), also known as Current Source Density (CSD) [148]. However, it is not clear which method could work better to find FC metrics. In a previous study, it was stated that SL filters were not able to distinguish between information coming from volume conduction or from real sources [149]. However, other authors are definitely in favour of using SL [150]. More, specifically, other study claimed the usefulness of SL to remove volume conduction in preparation of connectivity analysis [151]. In the case of FC metrics that ignore zero-phase-lag synchronizations, such as IC and WPLI, we assume that it is not necessary to perform a re-reference of the EEG data and therefore we will work with the original ear-referenced data.
- Choice of signal or source domain: a single EEG source can affect several electrodes at the same time, because of field spread effect of the EEG. Moreover, the conductivity of the human scalp produces the aforementioned problem of volume conduction. To mitigate these effects, it is necessary to perform a translation from signal to source domain, what is known as the "inverse problem". However, there is not a unique solution to this problem and, moreover, it is not possible to establish if the determined sources are reflecting true brain interactions [152]. This is why IC and WPLI emerge as useful metrics in the rehabilitation context, since they are insensitive to zero-lag

interactions and hence they assume that mapping between sensors and sources is instantaneous.

- Artifact rejection: this step has been performed by using the same method already described in chapter 3; therefore we are just going to mention it here. Firstly, power-line notch filter to remove the 50 Hz line interference; secondly a z-score procedure to remove trials with artifacts. Thirdly, a bandpass filter (between 0.1 and 50 Hz) to remove DC shifts and finally a CAR filter to deal with ocular movement artifacts. It is especially relevant when computing FC metrics that all applied filters are zero-phased, to avoid distortion of phase information.

3.2 Choice of epochs

There is a large range of values of epochs lengths in FC studies, from 1 second to a few minutes or even a day [146]. However, for phase synchronization metrics, longer epochs could result in lower FC values due to the asymmetry of phase distribution [146].

During the first trials with a BMI, there could be some seconds of poor concentration of the patients, since they are not accustomed to use a BMI. During the last trials, the patient could experience a certain fatigue, so we consider for the FC metrics the central trials. Therefore, we will take the 20 central trials, discarding the 10 initial ones and the 10 final ones.

3.3 Resting state vs task-related FC

Most of FC studies have been performed by means of fMRI. This technology involves a series of limitations, such as low temporal resolution (>1 s), as well as the spatial constraints imposed by the fMRI scanners, in which the subjects have to remain motionless during the recordings. This, together with the fact of the low number of time samples recorded by fMRI, makes difficult to study task-related FC changes during short tasks. Although resting-state FC has been shown as an effective method to assess changes in FC [36], [145], [153], in this study we would like to take the most of the EEG advantages by analyzing task-related FC. As other authors highlighted, clinical implications of task-related

FC changes have been rarely studied. Therefore, we will calculate FC during motor attempt of the upper limbs, namely during the 3 seconds after the cue appearance.

3.4 Choice of frequency bands

It has been already shown that lower (7-10 Hz) and higher (10-12 Hz) α bands are involved in cognitive processes [154]. For oscillations over 20 Hz in surface recordings, there are studies suggesting that they could be muscular artifacts [155], [156]. As there are not many studies about FC in SCI patients from EEG recordings, it is not clear which frequency band(s) could reveal more interesting information from brain interactions. In the study of Fallani *et al.*, the three classical EEG bands (θ, α and β) were used to determine FC. Therefore, in order to compare with that study and also considering that those frequency band have been broadly used to study different aspects of the brain, we decided to also use these frequency bands in our analysis.

3.5 Computation of metrics

Signal processing steps for each trial for Imaginary Coherence (IC) between two signals x and y. In the case of this study, x and y are two signals from 2 different EEG channels:

1. Zero-padding of x and y, because we are using convolution to smooth and, by default, it assumes that data outside the points we have are all zero.
2. Detrending of x and y.
3. Apply Hamming window to the detrended data.
4. Fast Fourier Transform (FFT) of the windowed signals.
5. Repeat step 4 for the whole signal, using a sliding window.
6. Calculate cross spectrum of x and y (S_{xy}) from spectrum of x (S_x) and spectrum of y (S_y):

$$S_{xy}(f)=x(f)\cdot y(f)^* \quad (4)$$

7. Calculate autospectrum of x and y:

$$S_{xx}(f)=|x(f)|^2 \qquad S_{yy}(f)=|y(f)|^2 \quad (5)$$

8. Apply time-frequency smoothing of the spectra (S_{xy}, S_{xx} and S_{yy}), by 2D convolution with a Gaussian kernel.

9. Calculate coherency from the smoothed spectra:

$$\boldsymbol{Cxy} = \frac{\boldsymbol{Sxy}}{\sqrt{\boldsymbol{Sxx} \cdot \boldsymbol{Syy}}} \quad (6)$$

10. Calculate imaginary part of C_{xy}.

11. Average per frequency bands (theta 4-7 Hz, alpha 8-12 Hz and beta 13-29 Hz).

Signal processing steps for each trial for the calculation of Weighted Phase Slope Index (WPLI):

1. Zero-padding of x and y, because we are using convolution to smooth and, by default, it assumes that data outside the points we have are all zero.
2. Detrending of x and y.
3. Apply Hamming window to the detrended data.
4. Fast Fourier Transform (FFT) of the windowed signals.
5. Repeat step 4 for all the signal, using a sliding window.
6. Calculate cross spectrum of x and y (S_{xy}) from spectrum of x (S_x) and spectrum of y (S_y), as in formula (4).
7. Apply time-frequency smoothing of the cross spectrum (S_{xy}), by 2D convolution with a Gaussian kernel.
8. Calculate WPLI from the smoothed spectrum:

$$\boldsymbol{WPLI} = \boldsymbol{Imag}\left(\frac{\boldsymbol{Sxy}}{|\boldsymbol{Sxy}|}\right) \quad (7)$$

9. Average per frequency bands (theta 4-7 Hz, alpha 8-12 Hz and beta 13-29 Hz).

The next procedure is common for both metrics: IC and WPLI. We computed both metrics on the after cue period, namely the interval of 3 seconds after the cue appearance, since we are interested in the neural interactions during the motor attempt phase of the BMI experiment. These steps are applied for each pair or EEG channels. After that, we have one value of IC and WPLI per frequency band and per pair of channels for each trial. Considering that there are 32 channels and both WPLI and IC are antisymmetric (i.e. IC between channel 1 and 2 will have the same value with opposite sign than IC between channel 2 and 1), we discarded the computation of the inverse metrics, then obtaining 496 combinations of each metric (IC and WPLI) between channels for each of the 3 frequency bands, giving a total number of 1488 IC metrics for each trial (IC matrix) and another 1488 WPLI (WPLI matrix).

As we have described in section 3.2, we will take the 20 central trials, discarding the 10 initial ones and the 10 final ones. We averaged IC and WPLI matrices for the 20 central trials, obtaining a single matrix for each session.

3.6 Global synchrony metric (GSYM)

As we have mentioned in the Introduction chapter, there are many different ways of measuring synchrony between brain areas, and within them, there are hundreds of possible combinations of frequency bands, epochs, etc. Then, one of the aims of this work is to design a method that comprises all this information in a single metric. We want to design a metric that could reflect the changes in brain interactions that could underlie functional recovery. Therefore, we studied which brain areas showed a FC more highly correlated with clinical scales already shown in Tables 3.6 and 3.8 from Chapter 3: GRASSP (items Strength, Prehension-Qualitative and Prehension-Quantitative) and SCIM. We designed a Global Synchrony metric (GSYM) that weighted and normalized this FCs in a single value. The weighted coefficients were taken from the Pearson correlation coefficient between the FCs and the clinical scales:

$$\boldsymbol{GSYM} = \frac{\boldsymbol{1}}{\boldsymbol{N}} \sum_{\boldsymbol{i=1}}^{\boldsymbol{N}} \boldsymbol{a_i} \cdot \boldsymbol{FC_i} \quad (8)$$

Where $\boldsymbol{a_i}$ are the weighting coefficients, FC_i is the value of the functional connectivity between two areas identified as correlated with clinical scales and N is the number of pairs of brain areas found highly correlated with clinical scales.

Before computing GSYM, it is necessary to pre-process FC by removing mean and shifting the values in such a way that all FC values are positive. Otherwise, adding up negative and positive terms would cancel the contribution of some of them. This pre-processing does not affect to the correlation since it does not change the waveform of the FC vectors.

3.7 Validation of GSYM

After calculating GSYM from EEG signals of the BMI+FES+VR experiments, we wanted to validate this metric in a different dataset, in order to study its applicability in different BMI experiments. To this aim, we calculated GSYM also in a set of EEG signals from experiments in which 4 SCI patients controlled a lower limb exoskeleton with a BMI. More details about these experiments were published in a work from our group [28]. The paradigm was similar to the one used in BMI+FES+VR, namely 3 seconds of motor attempt after the cue appearance. In this case, the cue was auditive, since the patient could not be focused on a screen because of the nature of the experiments. We used those 3 seconds interval from screening sessions to calculate GSYM. There were 40 trials of MA on each training session, and we calculated GSYM in the initial and final session performed by each patient, discarding the 10 initial and 10 final trials, as we did in the BMI+FES+VR experiments. In all screening sessions, the participants were standing, wearing the exoskeleton, and holding a walking aid, as can be seen in Figure 4.1. The patients could not actually move the legs during the screening blocks (as the exoskeleton joints were blocked). Therefore, they were attempting to perform the movement.

As the areas involved in motor attempt of the upper limb are not the same than the ones involved in motor attempt of the upper limb, we have to apply the same methodology described in the previous section, namely studying which brain areas showed a FC more highly correlated with clinical scales. In this case, clinical scales used were also different, since in these experiments both upper and lower limbs are involved, whereas in the BMI+FES+VR experiments only the upper limbs were involved. The clinical scales used for BMI+Exoskeleton experiments were: lower extremity motor score (LEMS), SCIM and 10 meter walk test (10MWT). LEMS was used to measure muscle strength, with 5 key muscles examined in each leg: hip flexors, knee extensors, ankle dorsiflexors, long toe extensors, and ankle plantar flexors. The grading system for the muscle strength goes from 0 to 5 (0 = absence of muscle contraction, 5 = normal active movement with full range of motion against full resistance). The cumulative score for the lower extremities ranges between 0 and 50. SCIM is a scale specifically designed to measure independence of SCI patients. It consists of 3 sub-items: self-care, mobility, and respiration and sphincter management [157]. 10MWT is a simple test in which the time to walk 10 meters is measured [158]. The scores obtained by patients ranged between 12 and 90 seconds. As we want to obtain values that increase with improvements of the user, we subtracted 100-10MWT [s]; in this way all the clinical assessments will increase with patient's improvements.

Fig 4.1 Patient carrying out a session with the BMI and the exoskeleton.

4. RESULTS

4.1 Neuroplasticity metrics for the BMI+FES+VR experiments

We were interested in observing which of the metrics could reflect clinically relevant information. Therefore, we calculated for all combinations of pairs of channels and frequency bands correlation between FC metrics (IC and WPLI) and clinical scales described in Chapter 3: GRASSP (items Strength, Prehension-Qualitative and Prehension-Quantitative) and SCIM. We compared initial and final clinical assessments with FC from first and last session for each patient. There were found 24 combinations that showed strong significant positive correlation between IC and clinical scales (considering strong as Pearson $r > 0.9$ with $p<0.001$), as can be seen in Table 4.1, and 20 combinations for WPLI, as can be seen in Table 4.2.

Results from IC and WPLI did not differ very much, since 16 of the combinations of between-channels FC that were found significantly correlated with clinical scales by WPLI were also found by IC. As IC provided a slightly higher number of correlated pairs, we selected this magnitude to design our own metric, GSYM. Therefore, according to the formula number (5), N was chosen as 24 and FC_i was the IC for each of the 24 combinations.

Using the IC between the identified areas shown in Table 4.2, we computed GSYM according to formula (5), obtaining an initial (PRE) and a final (POST) value of GSYM for each patient, as is shown in Fig. 4.2. PRE value represents the IC from the first session and POST from the last one.

GSYM scores were strongly correlated ($\rho=0.939$) with high significance ($p<0.001$) with Quantitative Prehension scale.

TABLE 4.1: Combinations of channels where IC showed strong positive correlation with clinical scales ($r > 0.9$ and $p<0.001$)

EEG Channel	EEG Channel	Frequency band	Clinical scale	ρ
CP4	T7	theta	strength	0.933
FC4	CP2	alpha	strength	0.956
FC4	CP4	alpha	strength	0.928
C5	Fz	alpha	strength	0.930
CP2	F7	alpha	PreQual	0.979
CP4	F7	alpha	PreQual	0.933
C5	Fz	alpha	PreQual	0.945
CP2	F3	beta	PreQual	0.929
C5	F8	alpha	PreQuan	0.934
C3	F8	alpha	PreQuan	0.976
AFz	C1	beta	PreQuan	0.986
AFz	CPz	beta	PreQuan	0.956
C5	Fz	beta	PreQuan	0.927
FP1	Fz	beta	PreQuan	0.957
F7	Fz	beta	PreQuan	0.959
FP1	F4	beta	PreQuan	0.966
C3	F8	beta	PreQuan	0.940
CPz	P7	beta	PreQuan	0.930
Fz	Pz	beta	PreQuan	0.926
FP2	P4	beta	PreQuan	0.957
F3	P4	beta	PreQuan	0.926
Fz	P4	beta	PreQuan	0.965
C2	O1	beta	PreQuan	0.926
CP4	FP2	alpha	SCIM	0.930

Freq. bands: theta 4-7 Hz, alpha 8-12 Hz and beta 13-29 Hz. Clinical scales: strength (GRASSP item), PreQual (Qualitative Prehension GRASSP item), PreQuan(Quantitative Prehension GRASSP item), SCIM (Spinal Cord Independence Measure)

4.2 Neuroplasticity metrics for the BMI+FES+Exoskeleton experiments

As we have described in section 3.7, in order to validate GSYM, the same methodology was applied to a different dataset: EEG data from BMI+Exoskeleton experiments. Clinical scores obtained by patients in this case are shown in Table 4.3.

TABLE 4.2: Combinations of channels where WPLI showed strong positive correlation with clinical scales (r > 0.9 and p<0.001)

EEG Channel	EEG Channel	Frequency band	Clinical scale	ρ
FC4	CP2	alpha	strength	0.935
CP2	F7	alpha	PreQual	0.934
CP4	F7	alpha	PreQual	0.959
F7	F3	alpha	PreQual	0.942
C5	Fz	alpha	PreQual	0.934
CP3	F4	alpha	PreQual	0.932
FC4	C6	beta	PreQual	0.942
CP2	F3	beta	PreQual	0.935
C5	F8	alpha	PreQuan	0.950
C3	F8	alpha	PreQuan	0.962
AFz	C1	beta	PreQuan	0.972
FP1	Fz	beta	PreQuan	0.957
F7	Fz	beta	PreQuan	0.927
FP1	F4	beta	PreQuan	0.966
CPz	P7	beta	PreQuan	0.939
AFz	Pz	beta	PreQuan	0.932
FP2	P4	beta	PreQuan	0.971
F3	P4	beta	PreQuan	0.941
Fz	P4	beta	PreQuan	0.953
CP4	FP2	alpha	SCIM	0.930

Freq. bands: theta 4-7 Hz, alpha 8-12 Hz and beta 13-29 Hz. Clinical scales: strength (GRASSP item), PreQual (Qualitative Prehension GRASSP item), PreQuan(Quantitative Prehension GRASSP item), SCIM (Spinal Cord Independence Measure)

Following the same methodology, we calculated the brain interaction more tightly related with patient's status. In this case, 6 interactions were identified, as is shown in Table 4.4.

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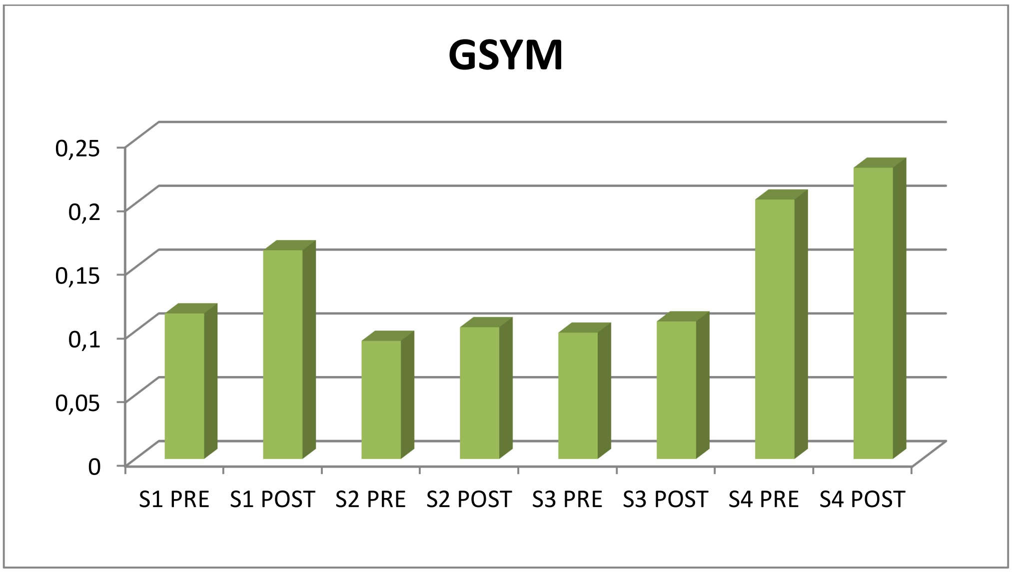

Fig 4.2 GSYM value before (PRE) and after (POST) BMI+FES+VR experiments for all subjects.

TABLE 4.3: Clinical scores obtain by the 4 subjects before and after the BMI+Exoskeleton

	S1		**S2**		**S3**		**S4**	
	PRE	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
Left LEMS	8	7	13	14	6	7	9	5
Right LEMS	12	11	8	9	11	9	19	21
SCIM-Personal care	16	16	15	15	12	12	17	13
SCIM-Mobility	20	18	19	21	16	19	21	19
100-10MWT score	58,47	54,137	79,067	87,01	63,017	77,203	26,007	10,19

PRE: before first session. POST: after last session. LEMS: Lower Extremity Motor Score. SCIM: Spinal Cord Independence Measure. 10MWT: 10 meter walk test

Using the IC between these areas, we computed GSYM according to formula (8), obtaining an initial (PRE) and a final (POST) value of GSYM for each patient, as is shown in Fig. 4.3.

TABLE 4.4: Combinations of channels where IC showed strong positive correlation with clinical scales (r > 0.9 and p<0.001)

EEG Channel	EEG Channel	Frequency band	Clinical scale	ρ
C3	T8	theta	Right Muscle Test	0,962
F8	T8	beta	Right Muscle Test	0,932
C1	O2	beta	SCIM-Personal care	0,933
FP1	FP2	theta	10MWT	0,928
CP2	T7	alpha	10MWT	0,977
C1	F3	beta	10MWT	0,927

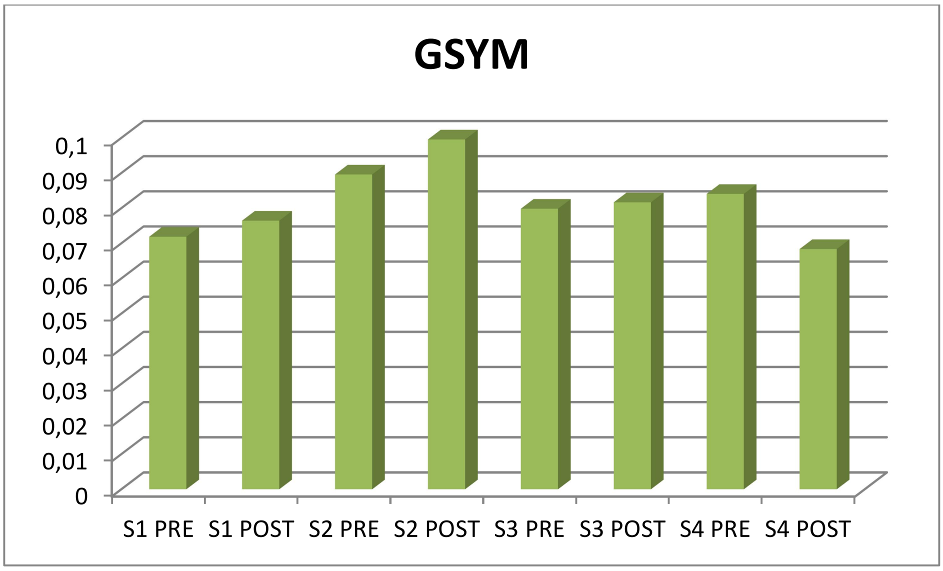

Fig 4.3 GSYM value before (PRE) and after (POST) BMI+Exoskeleton experiments for all subjects.

GSYM scores were strongly correlated (ρ=0.882) significantly ($p<0.05$) with left LEMS scale.

5. DISCUSSION

This is, to the best of our knowledge, the first study showing correlations between FC metrics calculated from EEG signals and clinical scales in patients with SCI after a BMI-based experimental therapy. We have shown that BMI can be used simultaneously to rehabilitate and evaluate patient's progress along the therapy, through FC metrics extracted from EEG signals. After studying the interactions between brain areas more directly related with functional recovery, we designed a metric that comprised all these interactions in a single value, weighted by the correlation coefficient of each of them.

Most of the correlations between FC metrics and clinical scales were found with respect to Quantitative Prehension item of GRASSP. This is an encouraging finding, since the main aim of the experiment described in Chapter 3 was to design a system able to promote recovery of grasping.

Interestingly, the IC between the pair of channels that most frequently appeared as correlated with clinical scores was in the pair C5-Fz, showing strong correlation in α band with strength, in α band with Qualitative Prehension and also in β band with Quantitative Prehension. C5 electrode is located in the motor cortex (M1) and Fz is located in the Supplementary Motor Area (SMA). Therefore, our result was consistent with previous findings from Hou *et al.*[141] , where they found in SCI patients from fMRI recordings that FC between M1 and SMA was correlated with functional recovery. Hence, we believe that it is feasible to obtain FC metrics from EEG recordings, with a cheaper and more portable technology implemented in a BMI.

The high similarity found between IC and WPLI indicated that both metrics are robust and can be used alternatively to assess FC in BMI studies. The difference between them is that WPLI is calculated using solely the imaginary part of the cross spectrum, while IC depends also on the amplitude of the individual spectrum, since it is normalized by them [130]. While IC is a linear metric, WPLI is non-linear. As we have shown, in the context of a BMI-based study, adding the non-linearity did not reveal new brain interactions. Our results then show that imaginary part of the spectrum offers a reliable metric, even in the presence of noise, of the synchrony between brain areas.

We have also shown that designing a new metric of global synchrony (GSYM) also reveals a neurophysiological assessment correlated with clinical status of patients. GSYM was strongly correlated with clinical scales (Quantitative Prehension in the case of BMI+FES+VR study and LEMS in the case of BMI+Exoskeleton). Even when brain areas involved in motor attempt of the upper and lower limbs are different, the methodology defined in this study allows calculating a single metric with clinical significance. It is also to the best of our knowledge the first study showing correlation of brain metrics with clinical status of patients before and after using an exoskeleton. There was just one study in which Youssofzadeh *et al.* found correlation between PDC and performance using the exoskeleton in healthy subjects [138].

It is interesting to highlight the robustness of the metrics against noise, since both have been applied in potentially noisy environments, specially the second scenario, in which patients are standing up and wearing a robotic exoskeleton. Since imaginary part of the spectrum is insensitive to zero-lag signals, the possible muscular artifacts are not affecting to the metrics.

Moreover, we believe that the methodology that we have described in this study could be useful to discriminate between FC changes due to brain reorganization that could be maladaptive, as other authors have suggested, and FC changes that are really reflecting a positive neuroplasticity [38]. It could allow the identification of FC changes directly related with clinical improvements.

We believe that the use of FC metrics in BMI studies could allow the clinicians evaluating patient's progress during the rehabilitation. It could also help to take decisions about going further or not with a particular neurorrehabilitative therapy. They are adding information about changes in brain synchrony, that could precede the functional recovery, as other authors have highlighted [159]. Additionally, the metrics could be used, with a larger database of patients, to perform patient segmentation, in order to assign the patient to a group and provide insight about which stage of the rehabilitation are the patients in, and then study the possibilities of success of BMI-based therapy. We claim that offering such information could narrow the existing gap between BMI research studies and real clinical applications.

6. CONCLUSIONS AND MAIN CONTRIBUTIONS

The conclusions and main contributions of this section of the thesis are:

1. The novelty of the application of FC metrics in the context of BMI-based experiments with SCI patients.
2. The design of a global metric of synchrony (GSYM) that comprises the interactions between brain areas more closely related with clinical status of the patients.
3. The definition of a methodology to extract clinically relevant information from EEG signals that could be applied in different scenarios, since the BMI+FES+VR and the BMI+Exoskeleton experiments described in this study.
4. Linear measurements of FC, such as IC, and non-linear, such as WPLI, reveal similar brain interactions in the context of a BMI study.
5. Imaginary part of the spectrum is a reliable way of determining neural interactions even in the presence of noise.
6. Surface EEG-based systems, despite its low spatial resolution, together with robust algorithms for data mining, offer an interesting tool to evaluate neuroplasticity, especially useful to develop neurorrehabilitation systems, due to its portability and non-invasiveness
7. There are significant correlations between brain interaction changes and physical status of patients with SCI, before and after BMI-based therapies: BMI+FES+VR and BMI+Exoskeleton.

CHAPTER 5: FUTURE WORK AND CONCLUSIONS

In this thesis, it has been demonstrated that Brain-Machine Interfaces and Virtual Reality can be useful for rehabilitation and also evaluation of patients. We have already written conclusions for each of the 3 chapters, but we summarize them in this final chapter:

- A new set of kinematic metrics to evaluate upper limb function by means of a virtual reality rehabilitation system has been designed.
- Clinical key features have been translated into mathematical formulations that comprise the kinematic data recorded by the inertial sensors.
- It has been shown that some of the defined kinematic metrics are correlated with standard clinical scales, therefore proving its clinical meaning.
- These metrics, together with the virtual reality system, offer the possibility of carrying out evaluation and therapy simultaneously, which is very important to refine patient's treatment.
- A method to minimize the influence of involuntary movements in the assessment of the agility has been defined by considering the relationship between the mean and the maximum angular velocity.
- BMI, FES and virtual reality have been successfully integrated as a system for therapy, allowing SCI patients to control both systems by themselves, without external assistance
- The system showed high levels of accuracy throughout the different sessions (79.13 % on average).
- The accuracy of the system in detecting motion intention remained stable throughout the different sessions, so we can conclude that the designed algorithms are sufficiently robust.
- Sparse discriminant analysis, a machine learning technique to reduce dimensionality and classify data, has been successfully applied to the BMI domain.
- Promising clinical outcomes have been obtained by 4 patients with iSCI after performing 5 therapy sessions with the system, as small improvements of their quantitative prehension in the stimulated arm compared with the non-

stimulated arm. Therefore, we conclude that the design of the system correctly accomplished the desired aims.

- The novelty of the application of FC metrics in the context of BMI-based experiments with SCI patients.
- A methodology to extract clinically relevant information from EEG signals that could be applied in different scenarios, since the BMI+FES+VR and the BMI+Exoskeleton experiments described in this study.
- A global metric of synchrony (GSYM) has been designed, comprising the interactions between brain areas more closely related with clinical status of the patients.
- Imaginary part of the spectrum has shown to be a reliable way of determining neural interactions even in the presence of noise.
- Surface EEG-based systems, despite its low spatial resolution, together with robust algorithms for data mining, offer an interesting tool to evaluate neuroplasticity, especially useful to develop neurorrehabilitation systems, due to its portability and non-invasiveness.
- There are significant correlations between brain interaction changes and physical status of patients with SCI, before and after BMI-based therapies: BMI+FES+VR and BMI+Exoskeleton.

We have identified several aspects that could be a matter of research for future studies:

- The set of metrics defined in Chapter 2 could be used in combination with the neuroplasticity metrics of Chapter 4, by the same group of patients. This experiment would be interesting to verify our hypothesis that the kinematic metrics are more tightly related with neuroplastic changes, since they address more specific aspects of patient's abilities than clinical scales.
- The sample of the BMI+FES+VR tests should be enlarged to confirm the promising results that the experimental therapy offered with 4 patients.

- In order to improve wearability of the designed systems, it would be interesting to study if other motion capture systems, such as Kinect, could be used to extract similar kinematic metrics, with the advantages of its lower cost and comfort for the user.
- New virtual reality headsets are being released very often, such as Oculus Rift or HTC Vive. It would be interesting to extend BMI+FES+VR with such headsets, in a more immersive scenario, that could open many possibilities for rehabilitation, such as designing therapeutic approaches combined with interactive videogames, to get the user more engaged and motivated.
- We have mentioned throughout the thesis the importance of low-cost in order to improve the acceptance of these experimental technologies in real clinical environments. Therefore, it would be very interesting to study the use of low-cost EEG recording systems, such as Emotiv or Neuroelectrics. Moreover, these devices do not require the application of conductive gel, which is one of the major drawbacks of BMI, according to the opinions of patients that we gathered in Chapter 3.
- Regarding functional connectivity (FC) techniques, we have shown the stability and robustness of imaginary spectrum strategies, as well as their correlation with the subjects' clinical status. Therefore, we believe that this kind of metrics should be used more frequently in BMI studies. There is still an existing gap between BMI research and real applications for patients, and one of the main reasons of this low acceptance is the lack of studies that show the real effects of the use of this technology in patients. Since one of the main arguments used to justify the goodness of BMI is that they are able to bridge lost connections of the neural system, it is essential to show the changes that the brain is undergoing. This includes not only amplitudes or intensity of signal in different areas, but also the interaction between them. This is what FC techniques allow; hence we emphasize their importance to add clinically relevant information to BMI investigation.
- Applying graph theory metrics, in combination with FC techniques, would allow studying the network structure of brain interactions in SCI patients. Other

authors have found, for example, that network efficiency is increased in SCI patients with respect to healthy ones (De Vico Fallani et al., 2007). It would be very interesting to investigate, in a long term period, the evolution of this network metrics and its relation with clinical status of patients.

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