



UNIVERSITAT DE
BARCELONA

Music-supported Therapy in the rehabilitation of motor deficits after stroke

Jennifer Grau Sánchez



Aquesta tesi doctoral està subjecta a la llicència **Reconeixement- NoComercial – SenseObraDerivada 4.0. Espanya de Creative Commons.**

Esta tesis doctoral está sujeta a la licencia **Reconocimiento - NoComercial – SinObraDerivada 4.0. España de Creative Commons.**

This doctoral thesis is licensed under the **Creative Commons Attribution-NonCommercial-NoDerivs 4.0. Spain License.**

Music-supported Therapy in the rehabilitation of motor deficits after stroke



Jennifer Grau Sánchez



UNIVERSITAT DE
BARCELONA

Doctoral Program in Biomedicine



UNIVERSITAT DE
BARCELONA

Music-supported Therapy in the rehabilitation of motor deficits after stroke

Jennifer Grau Sánchez

Cognition and Brain Plasticity Unit

Department of Cognition, Development and Educational Psychology

University of Barcelona

Supervisors:

Antoni Rodríguez Fornells

M^a Esther Duarte Oller

The research leading to these results has received funding from RecerCaixa.

Agradecimientos

Las palabras más difíciles de escribir son las que vienen a continuación. En septiembre de 2010 me uní a la Unidad de Cognición y Plasticidad Cerebral como técnica de laboratorio. Hacer balance de todo lo que ha ocurrido desde entonces hasta el depósito de la presente tesis en septiembre de 2018 requiere navegar por la memoria de una etapa que me ha transformado a nivel profesional y personal. Requiere sintonizar, reagrupar pedazos, rescatar y celebrar los buenos momentos y acariciar aquellos que fueron más difíciles. En todos estos momentos nunca me he sentido sola. Y es que este camino lo he recorrido acompañada de muchas personas que me han ayudado de diferentes formas. Decía que las palabras que vienen a continuación son las más difíciles de escribir. Y es que quisiera ser capaz de encontrar las palabras justas para agradecer y devolver todo el cariño que he sentido.

Mi más sincero y profundo agradecimiento se lo debo a mis directores de tesis, el **Dr. Antoni Rodríguez-Fornells** y la **Dra. Esther Duarte**. Me siento afortunada de haber trabajado bajo la dirección de dos personas a las que admiro.

Antoni, gracias por la oportunidad. De no ser por ti, no habría descubierto el apasionante camino de la investigación. Gracias por abrirme las puertas a este mundo, darme tiempo para explorar y animarme a saltar. Gracias por toda la confianza depositada en mí. Gracias por enseñarme, por exigirme y por darme espacio cuando lo he necesitado. Gracias por escucharme y por guiarme a lo largo de todos estos años. El principal responsable de que haya hecho de este camino mi vocación eres tú.

Esther, gracias por sumarte a esta aventura desde el principio. Gracias por tu confianza, por integrarme en tu equipo. Gracias por el día a día, por tener siempre un espacio para mí, por escucharme y enseñarme tanto. Gracias por tu mirada comprensiva y humana, por todos los consejos y por hacerme crecer como persona. Gracias por los buenos momentos y por los lugares que hemos visitado.

A mis compañeras **Nohora Rueda** y **Susana Redón**. Gracias por acompañarme, por animarme y cuidarme tanto. Gracias por todo vuestro trabajo en los estudios que forman esta tesis.

Gracias a la **Dra. Misericordia Veciana** y al **Dr. Jordi Pedro** del **Servicio de Neurología del Hospital Universitario de Bellvitge** por toda su implicación y trabajo en esta línea de investigación. Gracias por enseñarme con paciencia el funcionamiento del sistema nervioso a través de la Neurofisiología.

A lo largo de todos estos años mis días han transcurrido entre los pasillos del Hospital de l'Esperança y las salas del laboratorio de Bellvitge. Me siento afortunada de haber podido navegar entre estos dos mundos e integrar lo mejor de cada uno de ellos.

Gracias a los profesionales que forman el **Servicio de Medicina Física y Rehabilitación del Parc de Salut Mar - Hospital de l'Esperança**. En especial, gracias al **Dr. Ferran Escalada** por su apoyo a esta línea de investigación y por hacerme sentir que estaba en casa. A las doctoras **Roser Boza** y **Anna Guillén** por toda su ayuda. Gracias a la **Dra. Monique Messaggi-Sartor**, **Nuria Leiva** y **Sonia Nieto** por compartir mis inquietudes y animarme siempre.

Gracias a todos mis compañeros de **Brainvitge**. Brainvitge es un lugar especial, un universo paralelo lleno de seres únicos y brillantes con un talento increíble. Gracias por el compañerismo en los días de duro trabajo, las conversaciones diarias sobre ciencia, animales, política, filosofía y cultura en cada comida en el hospital, por la diversión en los bares y las noches surrealistas con la ciudad de Barcelona de fondo. Me gustaría agradecer especialmente a la **Dra. Estela Càmara** por su amistad y cariño, por enseñarme tanto. Por todas las discusiones sobre plasticidad, por hacerme reflexionar y crecer como científica. Gracias al **Dr. Josep Marco**, a la **Dra. Ruth de Diego** y al **Dr. Lluís Fuentemilla** por las palabras de ánimo y el feedback constructivo que he recibido durante estos años.

Gracias a **Joan Rodríguez** por su ayuda envuelta de paciencia infinita, las risas, el cariño y las salidas fotográficas. Gracias a **David Cucurell** por su capacidad de escuchar, su comprensión y por responder siempre desde el sentido común.

Gracias al **Dr. Julià Amengual** por ser la persona que me enseñó durante los primeros años de esta tesis. Gracias a mi amiga y compañera **Dra. Lucía Vaquero** por todas las conversaciones y consejos que me han ayudado a superarme.

Gracias a **Patricia León** por ser los ojos al otro lado de la pantalla. Gracias por tu amistad y por tu capacidad para hacerme sentir que todo va a salir bien. Gracias por los buenos momentos y por susurrar a pleno pulmón conmigo *'Haz que este baile merezca la pena'*. Gracias a **Berta Nicolás**. Gracias por tu amistad, por tu empatía y comprensión. Gracias por acompañarme y darme energía en los retos más difíciles. Por todo lo que te hace grande.

Gracias a la **Dra. Laura Ferreri** por tenderme siempre una mano amiga. Gracias al **Dr. Clément François** por ser la voz de la razón y darme los mejores consejos. Por ser el responsable de crear las noches más divertidas de Brainvitge. A **Neus Ramos**, gracias por ayudarme siempre. A la **Dra. Joanna Sierpowska** por su amistad durante estos años y su trabajo en los estudios de esta tesis. Al **Dr. Pablo Ripollés** por toda su ayuda y por su energía en hacer de Brainvitge ese lugar tan

especial. Gracias a **Alba Gómez** por hacer más divertido este último año. Al **Dr. Xavi Rifà** por su amistad. A la **Dra. Anna Martínez-Álvarez** por ponerme las gafas violeta y graduarlas cada tanto. Por inspirarme y hacerme crecer.

I would like to express my gratitude to **Dr. Teppo Särkämö** and **Dr. Mari Tervaniemi** for having me as a student at the **Cognitive Brain Research Unit of the University of Helsinki**. I had a wonderful and fulfilling experience at your Unit and my doctoral studies wouldn't be the same without the time I spent with you. Thanks to the people at the Unit for making me feel like I was at home. **Teppo**, thank you for teaching me, for all the discussions, for your kindness and patience. I feel so fortunate to have worked with one of the scientists I admire most. Thanks to **Dr. Aleksi Sihvonen** for his friendship and for being responsible of the best memories working at the lab.

Gracias a las **profesoras del Grado en Terapia Ocupacional de la Escuela Universitaria de Enfermería y Terapia Ocupacional de Terrassa**. En especial, gracias a **Betsabé Méndez** por todo el apoyo y aliento, por ser la primera persona que me ayudó a reconciliar dos mundos que parecían alejados. Gracias a **Carmen Moratinos** y a la **Dra. Loreto González** por los ánimos durante todos estos años y a **Pascale Pérez** por su amistad.

Gracias al **Col.legi de Terapeutes Ocupacionals de Catalunya** por su labor y por el apoyo a la investigación. A mis **compañeras de la Comisión para la creación del código deontológico** por los debates sobre ciencia, conocimiento y práctica clínica que me han ayudado a crecer e integrar otras miradas.

El último año como estudiante de doctorado tuve la suerte de participar en el **Junior Researcher Programme** y me siento profundamente agradecida por ello. Este programa me ha dado la oportunidad de liderar por primera vez un proyecto y me ha permitido conocer y trabajar con jóvenes investigadores de toda Europa. Algunos de ellos se han convertido en amigos. To my dearest friends, **Alina Cosma, Robert Blakey, Annika Nübold, Atar Herziger** and **Peter Edelsbrunner**. For their sincere friendship and all the good moments in different places. I had the opportunity to supervise an incredible team of young researchers, which whom I have learned so much and shared many good moments in the chaos of hard work and deadlines. To **Olatz Ojinaga, Renata Hlavová, Méabh Foley, Ilkka Muukkonen, Andrijana Radukić, Melanie Spindler**, and **Bodil Hundevad**.

Gracias a mis amigos. A **Arantxa Segovia, Melanie Barbancho, José Graus, Rodolfo Morrison, Nuria Espuny, Miriam Rigual** y **Clara Mercadé**. Thanks to **Johny Murphy** for his valuable help, support and advices. Gracias a **Ibán Grau** por estar siempre ahí. Gracias a **mi familia** por apoyarme y comprender mi trabajo. Gracias a **Joan Grau** y **Mireia Masferrer** por hacer

los domingos especiales y por escuchar con paciencia todas las historias que han rodeado esta tesis.

Este trabajo no habría sido posible sin el apoyo incondicional de mis padres, **Juan Grau y Esther Sánchez**. Muchas veces me encuentro en debates donde se apela a la igualdad de oportunidades para estudiar. Tengo muy presente que haber llegado hasta aquí es fruto de vuestro esfuerzo y sacrificio para que pudiera estudiar. Gracias por apostar e invertir en mi educación. Es el mejor regalo que me habéis podido dar. Me gustaría que sintierais esta tesis como vuestra. Sin vuestros valores y enseñanzas no habría podido recorrer este camino. Papa, gracias por enseñarme que la vida es más emocionante cuando te posicionas en los extremos. Gracias por ser un ejemplo de trabajo duro. Por inspirarme a ser responsable, ordenada y meticulosa. Mama, gracias por enseñarme que la vida está llena de matices. Gracias por tu humanidad y bondad infinita. Por inspirarme a ser mejor persona cada día.

Finalmente, me gustaría agradecer especialmente a todas las personas que han participado en los estudios de esta tesis. Gracias por confiar y aceptar el reto de participar aun cuando os encontrabais en uno de los momentos más difíciles. Gracias por dejarme ser testigo de la extraordinaria capacidad del ser humano para superarse y afrontar el reto de volver a aprender con optimismo y esperanza. Esperanza. Qué palabra tan bonita.

Badalona, septiembre de 2018

A mis padres

Table of contents

Abbreviations	15
Abstract	17
Resumen	21
Chapter 1. General introduction	27
1.1 Stroke as a public health priority.....	27
1.1.1 The global burden of stroke	27
1.1.2 Stroke pathophysiology	28
1.1.3 Continuum of stroke care.....	31
1.2 Stroke rehabilitation.....	33
1.2.1 From disability to functioning.....	33
1.2.2 Enhancing functioning through recovery and compensation.....	37
1.2.3 Mechanisms of neural plasticity.....	39
1.2.4 Time window of stroke recovery.....	50
1.2.5 Promoting plasticity through experience.....	52
1.2.6 Evidence-based therapies for motor deficits of the upper extremity.....	58
1.2.7 Developing new therapies in stroke rehabilitation.....	63
1.2.8 Interim summary: stroke rehabilitation.....	70
1.3 Music in stroke rehabilitation.....	72
1.3.1 Making music after stroke	72
1.3.2 Music-based interventions to treat motor deficits after stroke.....	75
1.3.3 Clinical questions.....	86
Chapter 2. Research aims	91
2.1 Study 1.....	91
2.2 Study 2.....	91
2.3 Study 3.....	92
2.4 Study 4.....	93
2.5 Summary of studies	93
Chapter 3. Study 1	99
3.1 Introduction	99
3.2 Methodology	102
3.2.1 Participants	102
3.2.2 Music-supported Therapy.....	104
3.2.3 Evaluation.....	105
3.2.4 Analysis.....	107
3.3 Results	108

3.3.1	Evaluation of motor function.....	108
3.3.2	Evaluation of quality of life.....	109
3.3.3	Evaluation of cortical excitability	109
3.4	Discussion	114
Chapter 4. Study 2	121
4.1	Introduction	121
4.2	Methodology	123
4.2.1	Study design.....	123
4.2.2	Participants	123
4.2.3	Randomisation.....	124
4.2.4	Treatment.....	124
4.2.5	Evaluation of participants.....	124
4.2.6	Blinding.....	126
4.2.7	Statistical analysis	126
4.3	Results	126
4.3.1	Demographic and clinical characteristics.....	126
4.3.2	Primary outcome	131
4.3.3	Secondary outcomes	131
4.3.4	Music reward experiences and response to Music-supported Therapy.....	138
4.4	Discussion	138
Chapter 5. Study 3	143
5.1	Introduction	143
5.2	Methodology	145
5.2.1	Participants	145
5.2.2	Design and treatment	146
5.2.3	Data acquisition.....	146
5.2.4	Lesion analysis.....	146
5.2.5	Experimental design.....	148
5.2.6	fMRI data analysis	148
5.3	Results	150
5.3.1	Demographic and clinical characteristics.....	150
5.3.2	Lesion analysis.....	155
5.3.3	fMRI results.....	158
5.4	Discussion	161
Chapter 6. Study 4	167
6.1	Introduction	167
6.2	Methodology	170

6.2.1	Participants	170
6.2.2	Experimental design.....	170
6.2.3	Music-Supported Therapy	171
6.2.4	Motor function assessment	172
6.2.5	Data analysis.....	174
6.3	Results	174
6.3.1	Clinical motor tests	174
6.3.2	3D movement analysis	178
6.3.3	Keyboard performance	181
6.4	Discussion	182
Chapter 7. General discussion		189
7.1	Music-supported Therapy and its effects on the motor function	190
7.1.1	Music-supported Therapy compared to conventional therapy	191
7.1.2	Effects on motor impairment and activity limitations.....	192
7.1.3	Time course of motor gains.....	194
7.1.4	Generalisation of motor gains to daily life activities.....	195
7.1.5	Retention of motor gains.....	197
7.2	Effects on cognition, mood and quality of life.....	198
7.3	The role of musical reward in Music-supported Therapy	200
7.4	Mechanisms of brain plasticity associated with Music-supported Therapy	201
7.5	Clinical considerations for implementation	204
7.5.1	Developing and redefining Music-supported Therapy.....	204
7.5.2	Piloting, feasibility and evaluating Music-supported Therapy.....	207
7.5.3	Reporting the results and implementing Music-supported Therapy	207
7.6	Strengths and limitations of the present work.....	208
7.7	Future directions in Music-supported Therapy research.....	211
7.7.1	Modifications to the protocol	211
7.7.2	Evaluation of patients.....	212
7.7.3	From the laboratory to the clinic	213
Chapter 8. Conclusions.....		217
References		221
Appendix		255
	Description of treatments.....	255
	Music-supported Therapy	255
	Conventional Therapy.....	256
	Description of measurements	259
	Neurological and functional evaluations.....	259

Motor function tests.....	260
Three-dimensional (3D) movement analysis measures.....	261
Cognitive function tests.....	262
Mood and quality of life tests.....	263
Transcranial Magnetic Stimulation measures.....	264
List of figures.....	265
List of tables.....	267

Abbreviations

3D	Three-dimensional
9HPT	Nine Hole Pegboard Test
AMT	Active motor threshold
APS	Arm Paresis Score
ARAT	Action Research Arm Test
BBT	Box and Blocks Test
BDNF	Brain-derived neurotrophic factor
CAHAI	Chedoke Arm and Hand Activity Inventory
CoG	Center of Gravity
CSP	Cortical silent period
EMG	Electromyography
FDI	First dorsal interosseous
FMA	Fugl-Meyer Assessment of Motor Recovery after Stroke
fMRI	Functional Magnetic Resonance Imaging
ICF	International Classification of Functioning, Disability and Health
MCID	Minimal clinically important difference
MDC	Minimal detectable change
MEPs	Motor-evoked potentials
MMSE	Mini-Mental State Examination
MRCS	Medical Research Council Scale
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PANAS	Positive and Negative Affect Scale
POMS	Profile of Mood States
QoL	Quality of life
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomised Controlled Trial
RMT	Resting motor threshold
TIDieR	Template for intervention description and replication
TMS	Transcranial Magnetic Stimulation
UE	Upper extremity
WHO	World Health Organization

Abstract

Motor deficits of the upper extremity are present in the majority of stroke patients, having a significant impact on their autonomy and quality of life. The recovery of motor deficits after stroke mainly relies on rehabilitation, which is a patient-centred process aimed at improving and maintaining the individual's functioning using therapeutic interventions to promote adaptive learning. Importantly, recovery will depend on the extraordinary ability of the nervous system to adapt to injury and the capacity of therapeutic interventions to induce brain reorganisation.

There are several techniques to treat the hemiparesis of the upper extremity after stroke, and recently, music-based interventions have emerged as a promising tool since they can incorporate many principles of stroke motor rehabilitation. Among them, Music-supported Therapy has been developed to enhance the motor function of the paretic upper extremity in stroke patients by playing musical instruments. Previous studies have shown that Music-supported Therapy can improve the functionality of the paretic upper extremity, promote functional neuroplastic changes and improve the mood and quality of life of subacute and chronic stroke patients. Despite these promising findings, Music-supported Therapy has not been appropriately contrasted with conventional therapy, and still, several aspects of its effectiveness remain unknown.

The main aim of this thesis was to study the effectiveness of Music-supported Therapy as a therapeutic intervention in the rehabilitation of upper extremity motor function after stroke. This thesis is composed of four studies that made use of different research designs and measurements at the neural, body functions, activity and participation level to address specific aspects that contribute to the effectiveness of Music-supported Therapy.

In **Study 1**, we tested the effectiveness of Music-supported Therapy in treating the hemiparesis of the upper extremity, inducing neuroplastic changes in the sensorimotor cortex and enhancing the quality of life in subacute stroke patients. We used an interventional experimental design where a group of subacute stroke patients received a four-week program of Music-supported Therapy in addition to the standard rehabilitation program. Patients were assessed before and after the treatment in an evaluation that comprised standardised clinical motor tests, an assessment of the excitability of the sensorimotor cortex with Transcranial Magnetic Stimulation and a quality of life questionnaire. In addition to the patients' group, a healthy group of matched controls underwent the same evaluation. The results of this study revealed that subacute stroke patients improved their motor function after the therapy and that this improvement was

Abstract

accompanied by changes in the excitability of the sensorimotor cortex and cortical motor map reorganisation. Furthermore, patients reported having a better quality of life after the treatment.

The aim of **Study 2** was to test the effectiveness of adding Music-supported Therapy to a standard rehabilitation program for subacute stroke patients. A randomised controlled trial was conducted in which patients were randomised into a Music-supported Therapy group or a conventional therapy group in addition to the standard rehabilitation program. Before and after four weeks of treatment, motor and cognitive functions, mood, and quality of life of patients were evaluated. A follow-up evaluation was performed at three months to test the retention of motor gains. Both groups significantly improved their motor function, and no differences between groups were found, indicating that Music-supported Therapy as an add-on treatment was not superior to conventional therapies for motor recovery. The only difference between groups was observed in the language domain for the quality of life. Further analysis revealed that patients treated with Music-supported Therapy improved their rate of verbal learning, reported less fatigue and negative emotions and experienced a better quality of life after the treatment. Importantly, the patient's intrinsic motivation to engage in musical activities was associated with better motor improvement in the Music-supported Therapy group.

In **Study 3**, a subsample of **Study 2** was evaluated with a structural and functional Magnetic Resonance Imaging protocol before and after the intervention. This study aimed to characterise the lesions and white matter damage of patients, test the relationship between corticospinal tract integrity and motor recovery and explore the mechanisms of brain plasticity induced by Music-supported Therapy in subacute stroke patients compared to conventional therapy. Patients in both groups of training presented lesions mainly at the subcortical level, and no differences were found in white matter damage between groups. We did not find any association between the proportion of disconnection of the corticospinal tract and motor improvement. The results of the functional imaging part of the study revealed that patients in the Music-supported Therapy group showed greater activations of the middle and superior temporal gyri and insula in the affected hemisphere during a motor task after the training.

In **Study 4**, we conducted a single-case design to explore the progression of motor improvements throughout the Music-supported Therapy sessions, examine the effects of a second period of training, study the retention of motor gains over time and investigate the generalisation of motor improvements to activities of daily living. A reversal design (ABAB) was implemented in a chronic stroke patient where no treatment was provided in the *A* periods, and a four-week program of Music-supported Therapy was applied in the *B* periods. Each period was comprised of four weeks, and an extensive evaluation of the motor function using clinical motor

Abstract

tests and three-dimensional (3D) movement analysis was performed weekly. During the Music-supported Therapy periods, a keyboard task was recorded daily to study the patient's musical task performance. A follow-up evaluation was performed three months after the second Music-supported Therapy period. Improvements were observed during the first sessions in the keyboard task, but functional motor gains were noticeable only at the end of the first treatment and during the second treatment period. These improvements were maintained in the follow-up evaluation. This study evidenced that gradual and continuous motor improvements are possible with the repeated application of Music-supported Therapy. Fast-acquisition in specific motor abilities was observed at the beginning of the Music-supported Therapy sessions, but generalisation of these improvements to other motor tasks took place at the end of the training or when another treatment period was provided.

Taken together, the results of this thesis show that Music-supported Therapy is an effective intervention in the rehabilitation of upper extremity function after stroke. Music-supported Therapy reduces the motor deficits and improves the functionality of the upper extremity in the same manner as conventional therapy, with gains that are generalised to activities of daily living and maintained over time. Moreover, patients treated with Music-supported Therapy have better language abilities, less fatigue and negative emotions, and greater quality of life than those patients treated only with conventional therapy. The pleasure experienced in musical activities is correlated with motor gains in patients treated with Music-supported Therapy, pointing out the importance of motivation in motor skill learning and stroke rehabilitation. Moreover, Music-supported Therapy promotes similar plastic changes than conventional therapy, inducing cortical motor map reorganisation and excitability changes in the sensorimotor cortex in stroke patients although further research is needed to pinpoint the neural plastic changes promoted by the therapy.

Resumen

Los déficits motores de la extremidad superior están presentes en la mayoría de los pacientes que han sufrido un ictus, e impactan de manera significativa en su autonomía y calidad de vida. La recuperación de los déficits motores después del ictus se consigue principalmente a través de la rehabilitación, que es un proceso centrado en la persona dirigido a mejorar y mantener la funcionalidad de esta a través de intervenciones terapéuticas para promover el aprendizaje adaptativo. Es importante destacar que la recuperación dependerá de la extraordinaria capacidad del sistema nervioso para adaptarse a la lesión y de la efectividad de las intervenciones terapéuticas en inducir reorganización cerebral.

Existen varias intervenciones terapéuticas para tratar la hemiparesia de la extremidad superior después del ictus. Recientemente, las intervenciones basadas en la música han surgido como una herramienta prometedora, ya que pueden incorporar muchos de los principios de la rehabilitación motora en ictus. Entre ellas, la Terapia con soporte Musical ha sido desarrollada para mejorar la función motora de la extremidad superior parética en el ictus mediante el uso de instrumentos musicales. Estudios previos han demostrado que la Terapia con soporte Musical puede mejorar la funcionalidad de la extremidad superior, promover cambios plásticos funcionales y mejorar el estado de ánimo y la calidad de vida de pacientes subagudos y crónicos que han sufrido un ictus. A pesar de estos hallazgos prometedores, la Terapia con soporte Musical no ha sido contrastada adecuadamente con la terapia convencional y todavía se desconocen algunos de los aspectos relacionados con su efectividad.

El objetivo principal de la presente tesis doctoral fue estudiar la efectividad de la Terapia con soporte Musical como intervención terapéutica en la rehabilitación de la función motora de la extremidad superior después del ictus. Esta tesis está compuesta por cuatro estudios que utilizaron diferentes diseños y evaluaciones a nivel neuronal, de las funciones del cuerpo, y de la actividad y participación de la persona y que tuvieron como objetivo abordar aspectos específicos que contribuyen a la efectividad de la Terapia con soporte Musical.

En el **Estudio 1**, evaluamos la efectividad de la Terapia con soporte Musical en rehabilitar la hemiparesia de la extremidad superior, inducir cambios neuroplásticos en la corteza sensoriomotora y mejorar la calidad de vida en personas que han sufrido un ictus. Utilizamos un diseño experimental en el que un grupo de pacientes subagudos recibió un programa de cuatro semanas de Terapia con soporte Musical además del programa de rehabilitación estándar. Los pacientes fueron evaluados antes y después del tratamiento en una evaluación que comprendía pruebas motoras clínicas estandarizadas, una evaluación de la excitabilidad de la corteza sensoriomotora a través de Estimulación Magnética Transcraneal y un cuestionario de calidad

Resumen

de vida. Además del grupo de pacientes, un grupo de controles emparejados se sometió a la misma evaluación. Los resultados de este estudio revelaron que los pacientes en fase subaguda del ictus mejoraron su función motora después de la terapia y que esta mejora fue acompañada por cambios en la excitabilidad de la corteza sensoriomotora y reorganización del mapa motor cortical. Además, los pacientes reportaron tener una mejor calidad de vida después del tratamiento.

El **Estudio 2** tenía como objetivo demostrar la efectividad de incorporar la Terapia con soporte Musical a un programa de rehabilitación estándar en pacientes de ictus subagudos. Se realizó un ensayo controlado aleatorizado en el que los pacientes fueron asignados al azar a Terapia con soporte Musical o terapia convencional, además de realizar el programa de rehabilitación estándar. Antes y después de cuatro semanas de tratamiento, se evaluaron las funciones motoras y cognitivas, el estado de ánimo y la calidad de vida de los pacientes. Se realizó una evaluación de seguimiento a los tres meses para investigar la retención de las mejoras motoras. Ambos grupos mejoraron significativamente su función motora, y no se encontraron diferencias entre grupos, lo que indica que la Terapia con soporte Musical no fue superior a las terapias convencionales en la recuperación motora. La única diferencia entre grupos se observó en la calidad de vida respecto al lenguaje. Análisis posteriores revelaron que los pacientes tratados con Terapia con soporte Musical mejoraron su ratio de aprendizaje verbal, refirieron sentir menos fatiga y emociones negativas y experimentaron una mejor calidad de vida después del tratamiento. Es importante destacar que la motivación intrínseca del paciente para participar en actividades musicales se asoció con una mayor mejoría motora en el grupo de Terapia con soporte Musical.

En el **Estudio 3**, una submuestra del **Estudio 2** fue evaluada con un protocolo de Resonancia Magnética estructural y funcional antes y después de la intervención. Este estudio tuvo como objetivo caracterizar las lesiones y el daño en la sustancia blanca de los pacientes, testear la relación entre la integridad del tracto corticoespinal y la recuperación motora y explorar los mecanismos de plasticidad cerebral inducidos por la Terapia con soporte Musical en comparación con la terapia convencional en pacientes en la fase subaguda del ictus. Los pacientes en ambos grupos presentaban lesiones principalmente a nivel subcortical, y no se encontraron diferencias en el daño de la sustancia blanca entre grupos. No encontramos ninguna asociación entre la proporción de desconexión del tracto corticoespinal y la mejoría motora. Los resultados de la parte de imagen funcional del estudio revelaron que los pacientes en el grupo de Terapia con soporte Musical mostraron una mayor activación en el giro medial y superior temporal y la ínsula del hemisferio afectado durante una tarea motora después del entrenamiento.

Resumen

En el **Estudio 4** utilizamos un diseño de caso único para explorar la progresión de las mejoras motoras en las sesiones de Terapia con soporte Musical, examinar los efectos de un segundo período de tratamiento, estudiar la retención de las mejoras motoras a lo largo del tiempo e investigar la generalización de la mejoría motora a las actividades de la vida diaria. Se utilizó un diseño de bloques (ABAB) en un paciente crónico donde no se proporcionó tratamiento en los períodos *A*, y se aplicó un programa de cuatro semanas de Terapia con soporte Musical en los períodos *B*. Cada período estuvo compuesto por cuatro semanas y se realizó una evaluación extensa de la función motora mediante pruebas clínicas y un análisis de movimiento tridimensional (3D) semanalmente. Durante los períodos de Terapia con soporte Musical, se registró diariamente una tarea con el teclado para estudiar el desempeño musical del paciente. Además, se realizó una evaluación de seguimiento tres meses después del segundo período de Terapia con soporte Musical. Se observaron mejoras durante las primeras sesiones en el desempeño con el teclado, pero la mejora en la función motora fue evidente solo al final del primer tratamiento y durante el segundo período de tratamiento. Estas mejoras se mantuvieron en la evaluación de seguimiento. Este estudio demostró que las mejoras motoras graduales y continuas son posibles con la aplicación repetida de Terapia con soporte Musical. La rápida adquisición de habilidades motoras es evidente en las primeras sesiones de Terapia con soporte Musical, pero la generalización a otras tareas tiene lugar al final o cuando se proporciona otro período de tratamiento.

Considerando los resultados en su conjunto, esta tesis muestra que la Terapia con soporte Musical es una intervención efectiva en la rehabilitación de la función de la extremidad superior después del ictus. La Terapia con soporte Musical reduce los déficits motores y mejora la funcionalidad de la extremidad superior de la misma manera que la terapia convencional, con mejoras que se generalizan a las actividades de la vida diaria y se mantienen a lo largo del tiempo. Además, los pacientes tratados con Terapia con soporte Musical tienen mejores habilidades lingüísticas, menos fatiga y emociones negativas, y una mayor calidad de vida que los pacientes tratados solo con terapia convencional. El placer experimentado en las actividades musicales se correlaciona con las mejoras motoras en pacientes tratados con Terapia con soporte Musical, señalando la importancia de la motivación en el aprendizaje motor y en la rehabilitación del ictus. Además, la Terapia con soporte Musical promueve cambios plásticos similares a la terapia convencional, induciendo reorganización del mapa motor cortical y cambios en excitabilidad de la corteza sensorimotora en pacientes que han sufrido un ictus, aunque investigaciones futuras son necesarias para identificar los mecanismos específicos de plasticidad cerebral promovidos por la terapia.

General introduction

Chapter 1. General introduction

1.1 Stroke as a public health priority

1.1.1 The global burden of stroke

Stroke is one of the most prevalent non-communicable diseases and a leading cause of mortality and acquired disability worldwide. In 2016 there were 79.5 million people affected by stroke globally, and among them, 13.6 million were new strokes (Figure 1, GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). In the last decade, the incidence has increased from 157.6 new cases per 100.000 inhabitants in 2006 to 185 in 2016 (Institute for Health Metrics and Evaluation, 2018). Stroke is also the second most common cause of death and years of life lost, only after ischaemic heart attack (GBD 2016 Causes of Death Collaborators, 2017). Around 5.5 million people died from a stroke in 2016, 310.000 of them in Western Europe (Figure 1, Institute for Health Metrics and Evaluation, 2018). Although stroke mortality has been reduced in developed countries in recent decades due to improvements in acute management (Feigin, Mensah, Norrving, Murray, & Roth, 2015), one-third of stroke survivors are often left with some form of disability making stroke the second cause of disability-adjusted lived years (GBD 2016 DALYs and HALE Collaborators, 2017).

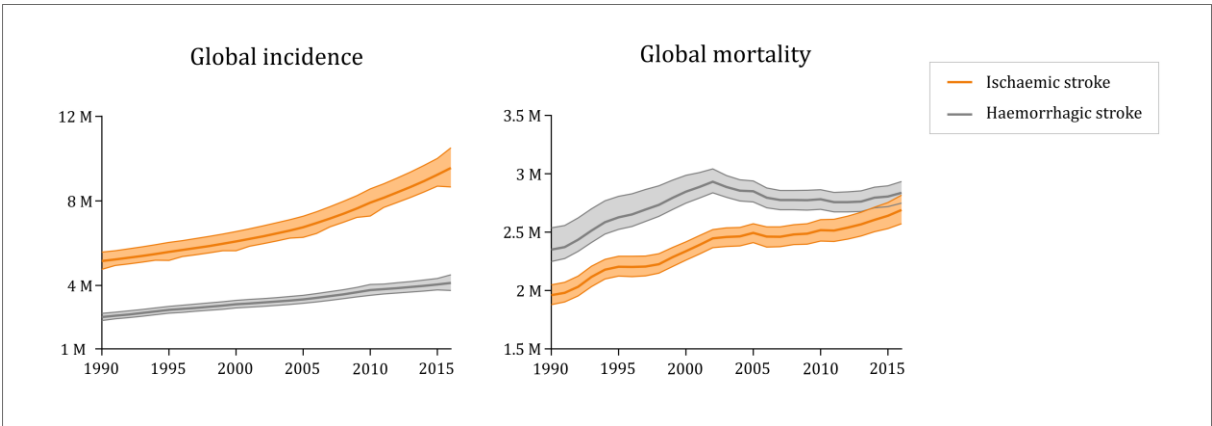


Figure 1. Stroke incidence and mortality. Global incidence and mortality for ischaemic and haemorrhagic stroke from 1990 to 2016 including both sexes and all ages. Data obtained from the Institute for Health Metrics and Evaluation (2018).

Behind these numbers, there are substantial geographical variations and societal changes occurring over time. The increase in the number of strokes is driven by the rapid ageing of the population, particularly in middle- and high-income countries with higher life expectancy (Truelsen et al., 2006). Contrary to the general belief that stroke is a disease of the elderly, two-

thirds of individuals affected by stroke are aged less than seventy (Feigin, Norrving, & Mensah, 2017). In developed countries, the presence of preventable risk factors such as low physical exercise, poor dietary habits, tobacco use, and drug abuse raises stroke incidence (Feigin et al., 2017). In the European Union, new cases of strokes are expected to increase 34% by 2035 (Stevens, Emmett, Yanzhong, McKeivitt, & Wolfe, 2017). The rapid ageing of population, together with the increment of risk factors related to lifestyle habits and the decline in stroke case-fatality will result in a higher proportion of stroke survivors who will need inpatient care, rehabilitation and long-term care and support. It is estimated that €45 billion is currently spent on stroke care in Europe, including the cost of medical care and the indirect cost of productivity loss due to death and disability (Stevens et al., 2017). Taken together, stroke represents one of the biggest societal and economic public health challenges worldwide (Feigin et al., 2017; Truelsen, Ekman, & Boysen, 2005).

1.1.2 Stroke pathophysiology

The World Health Organization (WHO) defines *stroke* as '*a clinical syndrome consisting of rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin*' (Hatano, 1976). There are two types of stroke: ischaemic and haemorrhagic. In ischaemic stroke, the occlusion or obstruction of a vessel leads to an interruption of the cerebral blood supply whereas in haemorrhagic stroke a vessel rupture causes bleeding (Rodgers, 2013). Besides this general distinction, strokes can also be classified by aetiology and location.

1.1.2.1 Classification of strokes by aetiology

Establishing the cause of stroke is critical to decide on treatments and prevention of recurrent strokes. Regarding ischaemic stroke, several factors including atherosclerosis and embolism can cause the interruption of blood supply. Atherosclerosis is a condition in which the artery narrows locally by an atherosclerotic plaque that can compromise blood supply (Ross, 1993). Atherosclerotic plaques can also segment and travel through the artery to more distant regions and disturb the blood flow of a healthy branch, becoming an artery-to-artery embolism (Wong, Caplan, & Kim, 2016). Blood clots can be formed in the heart due to atrial fibrillation, travel to the brain and block blood flow, which is known as cardioembolic stroke (Kim, 2014). These mechanisms usually occlude the main cerebral arteries, but deep perforating branches can also harden and lose elasticity and thus interrupt the blood supply to small regions in the brain (Wiseman, Marlborough, Doubal, Webb, & Wardlaw, 2014). In some cases, ischaemic strokes can be explained by unusual causes such as vasculopathies or hematologic disorders. In other cases,

it may not be possible to determine the source of a stroke with any degree of confidence despite an extensive evaluation. All these causes are included in the TOAST classification, which distinguishes ischaemic strokes causes into i) large-artery atherosclerosis, ii) cardioembolism, iii) small-artery or lacunar occlusion, iv) stroke of other determined aetiology, and v) stroke of undetermined aetiology (Adams et al., 1993). Haemorrhagic stroke is usually caused by uncontrolled hypertension, aneurysms and arteriovenous malformations, which rupture blood vessels and lead to bleeding (Aronowski, Wagner, Xi, & Zhang, 2016).

Although the mechanisms of ischaemic and haemorrhagic strokes differ, the ultimate consequence is that neural and tissue necrosis occurs in the brain region irrigated by the affected vessel (Ay, 2016). The death of neuronal populations leads to disturbances of neurological functions and deficits of motion, sensation, perception, cognition and emotion can manifest in individuals who have suffered a stroke (Rathore, Hinn, Cooper, Tyroler, & Rosamond, 2002). The appearance of one deficit or a combination of them depends on the anatomical location of the stroke.

1.1.2.2 Classification of strokes by anatomical location

The anatomical classification of ischaemic strokes follows the architecture of the arteries that irrigate the brain, brainstem and cerebellum, defining the vascular territories. Brain irrigation can be divided into anterior and posterior circulation, responsible for 80 % and 20% of blood flow to the brain, respectively. The Oxfordshire Community Stroke Project Classification is a widely used tool to differentiate ischaemic stroke into total or partial anterior circulation stroke, posterior circulation stroke or lacunar stroke (Bamford, Sandercock, Dennis, Warlow, & Burn, 1991).

The anterior circulation includes the carotid arteries and the middle and anterior cerebral arteries. The middle cerebral artery irrigates cortical and subcortical regions of the frontal, parietal and temporal lobes (Figure 2). A stroke in the proximal segment of this artery will manifest as hemiplegia or hemiparesis, hemisensory loss, gaze deviation, and aphasia or neglect. A stroke in distal segments will result in more pronounced hemiparesis of the face and arm rather than the leg or hemianopsia (Sharma & Wong, 2016). Since the middle cerebral artery originates from the carotid artery, a stroke located in the latter will lead to the same clinical deficits as a stroke in the proximal segments of the middle cerebral artery. The anterior cerebral artery supplies blood to the midline region of the frontal lobe and the superior medial parietal lobe. Strokes in this artery are less common because the irrigation of blood can be compensated by collateral communication if there is an occlusion. Nevertheless, when they occur they can

provoke hemiparesis and sensory loss mainly in the lower extremity (Brust & Chamorro, 2016; Liebeskind, 2003; Perlmutter & Rhoton, 1976).

The posterior circulation is composed of the vertebral and basilar arteries, and the posterior cerebral artery, which supplies blood to the brainstem, cerebellum and occipital lobe (Figure 2). When the stroke is located in the vertebrobasilar system and affects the brainstem, it can manifest as loss of consciousness, cranial nerve deficits, apnea and cardiovascular instability among other deficits whereas a stroke in the cerebellum can provoke dizziness, ataxia and motor coordination problems (Choi, Lee, & Kim, 2013; Kim & Caplan, 2016). Posterior cerebral artery strokes can lead to homonymous hemianopsia and sometimes amnesia (Kim, 2016).

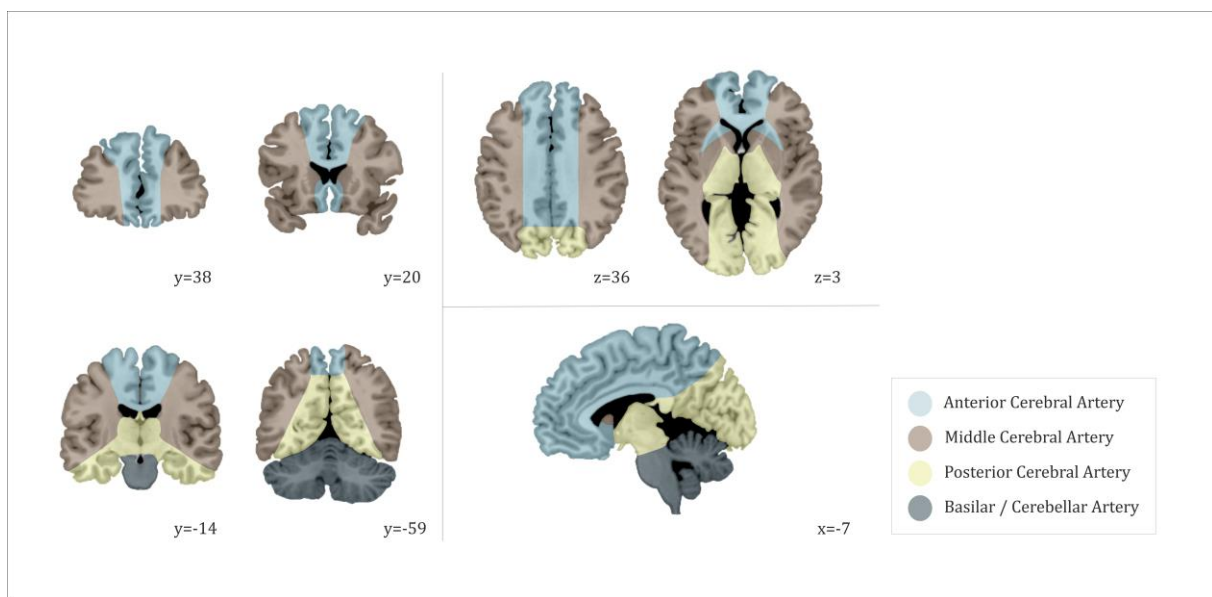


Figure 2. Vascular territories of the brain, brainstem and cerebellum.

Vascular territories of the main cerebral arteries (anterior, middle, and posterior cerebral arteries) and arteries irrigating the brainstem and cerebellum (basilar and cerebellar arteries). Adapted from Moeller & Reif, 2013.

Strokes can also occur in the perforating branches that come from the main cerebral arteries. These strokes are known as small vessel or lacunar strokes because these deep perforating branches irrigate smaller regions of the brain (Pantoni, 2010). Lacunar strokes usually take place in the lenticulostriate or thalamic arteries affecting the basal ganglia, the internal capsule, the periventricular white matter or the thalamus and leading to pure motor or sensory deficits (Pantoni, 2010; Wiseman et al., 2014).

The anatomical classification of haemorrhagic strokes takes into account whether the stroke has occurred in the parenchyma or the subarachnoid space (Aronowski et al., 2016). A haemorrhagic stroke in the parenchyma can affect cortical and subcortical regions, sometimes occupying or displacing the ventricular system (Larrue, Von Kummer, Müller, & Bluhmki, 2001; Paciaroni et

al., 2008). Subarachnoid haemorrhages, located between the meninges arachnoid and pia matter, are often considered separately in research since the clinical manifestations and the prognosis differ from intraparenchymal haemorrhages.

1.1.2.3 Risk factors for stroke

The risk of stroke increases with age, which has a complex interplay with gender. Men are more likely to have strokes than women. However, since women have a higher life expectancy, they tend to have more strokes at an older age, which are in turn more severe (Barker-Collo et al., 2015; Dehlendorff, Andersen, & Olsen, 2015; Haast, Gustafson, & Kiliaan, 2012). Regarding ethnicity, the risk of stroke is higher for young black men compared to other ethnic groups (Howard, 2013). Together with diabetes, age, sex and ethnicity are non-modifiable factors. However, hypertension, smoking, cardiac disease, carotid disease, hyperlipidaemia, and alcohol consumption also increase the risk of having a stroke but are modifiable factors (Feigin et al., 2017; Krishnamurthi et al., 2013). Stroke is preventable, however, when it occurs, it has devastating consequences for neurological functions and can lead to death. Most individuals who have suffered a stroke will need medical and social services for a year, and many will require assistance for life (Rodgers, 2013).

1.1.3 Continuum of stroke care

Since stroke is a medical emergency that occurs suddenly, it is of paramount importance that everybody is able to recognise the symptoms and seek immediate medical assistance. Public education campaigns are aimed at raising stroke awareness and decreasing the time window between stroke onset and acute management at a stroke unit (Flynn et al., 2014; Mellon, Hickey, Doyle, Dolan, & Williams, 2014). The reduction of this time window is critical to improve outcomes and avoid death (Ringelstein et al., 2013). Usually, the first health professionals who attend the stroke patient are paramedics, emergency staff and primary care physicians. They screen the patient and refer them to the nearest stroke unit or centre, with rapid transportation and pre-hospital notification (Jauch et al., 2013).

Upon arrival to the hospital, the stroke patient should be neurologically evaluated by a physician, and a neuroimaging evaluation should be performed within the first 30 minutes of hospital admission (Fonarow et al., 2011). The stroke unit is a specialised ward which aims to ensure vital functions, monitor the patient, diagnose and apply stroke-specific therapeutic interventions, start secondary prevention and provide early mobilisation and rehabilitation (Ringelstein et al., 2013). The stroke unit is made up of a multidisciplinary team including physicians, nurses,

physiotherapists, occupational therapists, speech therapists, neuropsychologists and social workers with training and expertise in stroke management who should meet regularly to align objectives and strategies (Rodgers & Price, 2017). During hospitalisation, the patient should start receiving daily rehabilitation with early mobilisation within the first 24 to 72 hours if the vital signs are stable and the condition of the patient allows it (Ringelstein et al., 2013). The results from the AVERT trial indicated that frequent and short sessions facilitating the mobility of the patient in out-of-bed activities reduced disability at three months post-stroke (Bernhardt et al., 2016). Patients treated in stroke units have less case-fatality and dependency than patients treated in general medical or neurological wards (Langhorne, O'Williams, Gilchrist, & Howie, 1993; Stroke Unit Trialists' Collaboration, 2013). Only 30% of stroke patients in Europe are treated in stroke units despite evidence supporting the organised stroke care and the recommendations of the European Stroke Organization (Ringelstein et al., 2013; Stevens et al., 2017).

After discharge from the stroke unit or the acute hospital, more than two-thirds of stroke patients will need some form of rehabilitation. Depending on the consequences of the stroke, the patient may need physical and occupational therapy, cognitive rehabilitation or speech therapy (Krakauer, Carmichael, Corbett, & Wittenberg, 2012; Winstein et al., 2016). Rehabilitation services and programs vary across countries and even regions within the same country in the type of setting, duration, intensity and health professionals involved (Winstein et al., 2016). Furthermore, stroke patients may undergo multiple transitions in care given the different levels of organisation in rehabilitation, which is a challenge when ensuring continuity in rehabilitation objectives and treatments.

The post-acute inpatient care services for stroke patients include rehabilitation facilities and long-term care hospitals. Inpatient rehabilitation facilities usually offer an intensive program with at least 3 hours of therapy per day under the supervision of a medical doctor specialised in physical medicine and rehabilitation (Ringelstein et al., 2013). Early supported discharge is particularly recommended for patients with mild to moderate deficits as a service aimed to improve the transition between hospital and the patient's home and offer rehabilitation in the home setting or the community (Rodgers & Price, 2017). A recent meta-analysis found that patients receiving early supported discharge were more independent in activities of daily living than patients who received conventional rehabilitation services (Langhorne, Baylan, & Early Supported Discharge Trialists, 2017). After discharge from the inpatient rehabilitation hospital, community-dwelling stroke patients may receive outpatient rehabilitation at home or in day hospital services (Hillier & Inglis-Jassiem, 2010; Outpatient Service Trialists, 2003). Long-term care facilities admit patients with severe deficits, who need extended medical care and are not

able to return home (Crocker et al., 2013; Pereira et al., 2012). The rehabilitation of the stroke patient will last for several months and should incorporate a community-reintegration model to return to work, do leisure activities and exercise for fitness (Winstein et al., 2016). At the end of the rehabilitation process, the stroke patient should receive follow-up reviews and might be referred to stroke support organisations (Stevens et al., 2017).

1.2 Stroke rehabilitation

The WHO defines *rehabilitation* as ‘a process aimed at enabling people with disabilities to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels, providing them with the tools to attain independence and self-determination’ (United Nations, 2006). The principal aim of rehabilitation is to improve and maintain functioning at many different levels, through restitution, substitution and compensation of functions. Rehabilitation is a patient-centred process, with progressive, dynamic and cyclic stages that include i) evaluation of patient’s needs, ii) collaborative goal setting, iii) therapeutic interventions, and iv) reevaluation (Langhorne, Bernhardt, & Kwakkel, 2011). Since there are many different levels of functioning, interventions can be biomedical, psychological, social, educational and vocational, and are provided by a multidisciplinary team (Kwakkel, Kollen, & Lindeman, 2004). One of the critical aspects of stroke rehabilitation is that recovery at the behavioural level will depend on the extraordinary ability of the nervous system to adapt to injury. This ability is known as neuroplasticity or neural plasticity, reflecting the malleable nature of the nervous system and the capability of change after an injury or in response to therapy (Cramer et al., 2011). Stroke rehabilitation aims to promote neuroplasticity to achieve the highest possible level of functional recovery (Krakauer et al., 2012).

The following sections review the levels of functioning and distinct forms to improve functionality, the mechanisms of neuroplasticity, the timeline of stroke rehabilitation, principles for training, and evidence-based therapies to restore motor deficits. Finally, methodological aspects in the field of stroke rehabilitation research are reviewed.

1.2.1 From disability to functioning

Disability is a complex phenomenon; it is a result of the interaction between the individual affected by a disease and the environment in which the person lives. Classically, the medical model viewed disability as a consequence of the health condition of the person (Brisenden, 1986). On the contrary, the social model attributed a person’s disability to the environmental demands of a society that was unaccommodating for people that had specific health conditions

(Oliver, 1996). The biopsychosocial model integrates both the medical and social models and might be more comprehensive in the understanding of disability and its causes (Alford et al., 2015). The WHO adopted this model in its International Classification of Functioning, Disability and Health (ICF, World Health Organization, 2001). The ICF provides a framework for understanding functioning and disability as an interaction between health conditions and contextual factors that affect body structure and function, the activities that the person does and the participation of the person in everyday life (Figure 3).

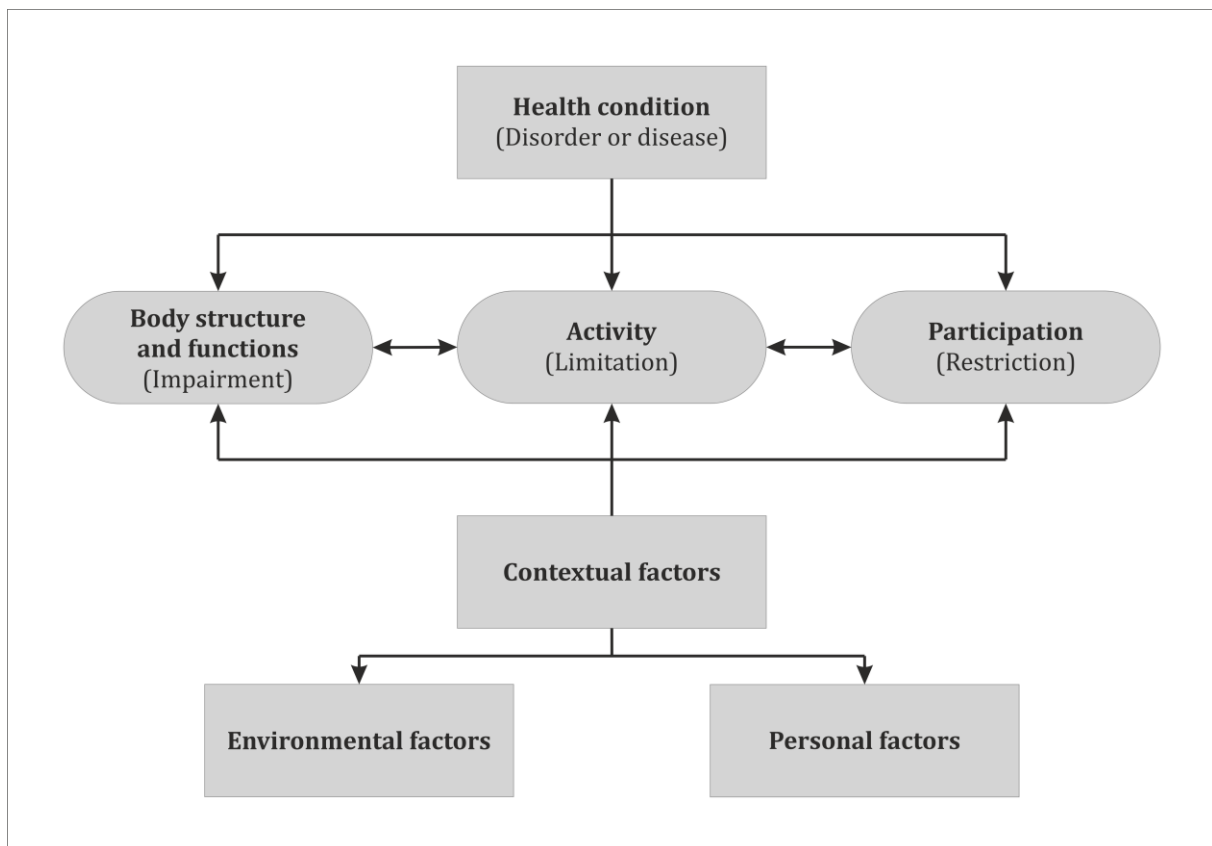


Figure 3. International Classification of Functioning, Disability and Health.

Human functioning can be described at the level of body structure and its function, activity and participation. Alterations in these levels of functioning are known as impairments, limitations and restrictions. Functioning is influenced by health condition and contextual factors, which are divided into environmental and personal factors. Adapted from World Health Organization, 2001.

The ICF distinguishes three levels of functioning: the body, activities and participation of the person in a real life situation.

In the case of stroke patients, neural and tissue death occur after injury, altering or disrupting neurological functions. For instance, a stroke in the primary motor cortex leads to contralateral muscle weakness and decreased motor control (Sharma & Wong, 2016). Stroke is a health condition or disease that causes damage to the brain (*body structure*) and leads to movement problems (*body function*). The alteration in body structure and functions is known as

impairment or deficit. Motor deficits of the upper limb include paresis, spasticity, and poor spatiotemporal coordination, usually decreasing the ability to reach, grasp and manipulate objects (Jones, 2017).

When functional movements are impaired, tasks such as tying a shoelace or drinking from a glass will be affected, having an impact on the individual's autonomy in the activities of daily living; in this example, it would be getting dressed and eating. The ICF defines the inability or difficulty in executing activities as limitations. It is well documented that, after a stroke, motor deficits highly correlate with limitations in activities of daily living (Wade & Hower, 1987). Between 55% and 75% of stroke patients experience limitations in the functional use of the upper extremity, which decreases their level of independence and health-related quality of life (Carod-Artal, Egido, González, Varela de Seijas, & Seijas, 2000; Mayo, Wood-Dauphinee, Carlton, Durcan, & Carlton, 2002; Mutai, Furukawa, Nakanishi, & Hanihara, 2016; Olsen, 1990).

Going out for dinner with friends is a social leisure activity that reflects participation in a real life situation. It might require getting ready for the meeting, driving or using public transport safely, eating independently and socialising. A stroke patient facing difficulties in getting dressed, eating, community mobility and maintaining complex interpersonal interactions may also show restrictions in participation. Nevertheless, participation is more complex than just executing a set of activities. Participation depends on body functions, task features and social and physical environments but goes beyond that in a way that it reflects the fulfilment of personal goals and social roles and thus, the performance at the societal level (Perenboom & Chorus, 2003; Whiteneck & Dijkers, 2009). A survey in a cohort of stroke survivors found that 65% of respondents suffered restrictions in their reintegration into community activities after stroke (Mayo et al., 2002). In working-aged adults who have suffered a stroke, social consequences in family relationships, sexual life, return to work, domestic economy and leisure activities have been reported (Daniel, Wolfe, Busch, & Mckevitt, 2009). Restrictions on participation affect quality of life and life satisfaction (Algurén, Fridlund, Cieza, Sunnerhagen, & Christensson, 2012; Mayo, Bronstein, Scott, Finch, & Miller, 2014). Quality of life is defined as *'the individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, standards and concerns'* (World Health Organization Quality of Life Group, 1998). Quality of life is a broad concept characterised by the individual's health, psychological state, personal beliefs, social relationships and their relationship to their environment (World Health Organization Quality of Life Group, 1998). Specifically, health-related quality of life is a construct to define how the individual's perception of their position in life is modified by impairments and functional status, and influenced by disease, injury, treatment and policy (Patrick & Erickson, 1993). Besides improving body functions and

autonomy in activities of daily living, one of the aims of rehabilitation is to achieve the patient's reintegration into community life and enhance quality of life (Albert & Kesselring, 2012).

These three levels of functioning (the body, activities and participation) are influenced by the context in which the person lives. Contextual factors in the ICF refer to personal and environmental factors, which may interact with the health condition complexly, facilitating or hindering functioning (Vargus-Adams & Majnemer, 2014; Wang, Badley, & Gignac, 2006). On the one hand, personal factors are elements of the person such as gender, age, education, profession, socioeconomic status, coping style, personality, lifestyle preferences or pattern of behaviour among other factors that shape how the person experiences disability (Alford et al., 2015). Personal factors are the only element within the ICF that is not coded given its idiosyncrasy. On the other hand, environmental factors include physical and societal elements which range from physical barriers or facilitators to legal, governmental and social structures (Alford et al., 2015). Contextual factors may have confounding, moderating or mediating effects on the functioning (Table 1).

Table 1. Levels of functioning influenced by a stroke.

Patient: Alicia, 63 years old			
Body structure and Body functions	Activity and Participation	Personal factors	Environmental factors
Ischaemic stroke in the left middle cerebral artery, affecting the left motor cortex.	Limitations in getting dressed, personal hygiene and eating independently.	Eager to improve and be independent.	Solid family support. Insurance covers assistive devices.
Weakness of the right upper extremity.	Limitation in mobility. Unable to return to work.	Afraid of falling.	Public health system provides rehabilitation. Physical barriers at home (stairs).
Weakness of the right lower extremity.	Unable to take care of grandchildren.	Anxious about retirement.	Son concerned of not getting her help with his children in the future.

Representative case of a patient who suffered an ischaemic stroke. Elements of the patient's functioning at the body, activity and participation level, and environmental and personal factors are described.

Functionality is affected by numerous personal and environmental factors, and thus, disability experiences depend on the individual's circumstances. The ICF has promoted a shift in the hospital-based paradigm focused on diagnosis and deficits to a more comprehensive and holistic understanding of the person experiencing disability (Bickenbach, 2012).

1.2.2 Enhancing functioning through recovery and compensation

The terms *recovery* and *compensation* are often used in neurorehabilitation as distinct forms to achieve functionality. Rehabilitation of the neurological patient is aimed at regaining functions that were present before the brain injury or maximising the remaining resources to achieve functionality (Selzer, Clarke, Cohen, Duncan, & Cage, 2006). Recovery means functioning as in the same way before the stroke, in other words, returning towards a regular pattern of behaviour. Compensation, on the contrary, is focused on achieving a goal using a new approach with the functions that are preserved (Bernhardt et al., 2017).

In the case of the motor system, at the body function level, recovery is the reappearance of elemental motor patterns during task accomplishment. It requires the reacquisition of premorbid patterns of movements using the same effectors and joints as a healthy individual in a given task (Levin, Kleim, & Wolf, 2009). For instance, to reach and grasp an object, shoulder and elbow extension are required together with a direct trajectory of the forearm towards the target object. To grasp the object, the wrist needs to be stabilized, and a slight extension of fingers is required followed by flexion around the object with the precise grip force to lift the object (Figure 4A).

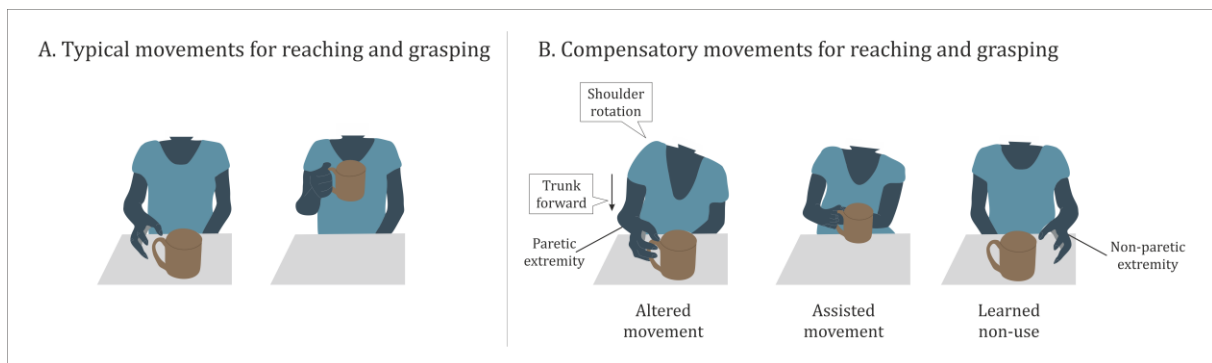


Figure 4. Typical and compensatory movements for reaching and grasping.

A) Typical movements to reach and grasp an object. B) Compensatory movements to reach and grasp an object. The shoulder and trunk can compensate to reach the object in an altered form, the non-paretic limb can assist the paretic limb, or the movement can be performed solely by the non-paretic limb. Adapted from Jones, 2017.

Although there are multiple combinations of muscle synergies and joint movements when doing this simple and apparently effortless task, movements need to be performed in the most cost-effective manner with a reliance on visual and somatosensory feedback. A well-recovered stroke patient will reach and grasp an object in the same way a healthy individual does. The normalisation of movements is evidenced as an increase in degrees of freedom and peak velocity.

Moreover, in recovered patients, there is a reduction of errors and compensatory movements with the shoulder and trunk (Duff et al., 2013; Van Kordelaar, Van Wegen, & Kwakkel, 2014).

In compensation, novel motor patterns appear during the task and can include using the remaining motor elements in an altered form (*adaptive compensation*) or using alternative effectors and joints (*substitutive compensation*, Levin et al., 2009). A stroke patient showing compensation in reaching and grasping an object may use the trunk and shoulder to stabilise and control the hand, or use the non-paretic side to assist the affected limb or perform the task (Figure 4B, Jones, 2017; Levin, Michaelson, Cirstea, & Roby-Brami, 2002; Michaelson, Jacobs, Roby-Brami, & Levin, 2004). Whereas recovery requires some neural repair, compensation requires learning new strategies (Bernhardt et al., 2017).

The constructs *recovery* and *compensation* can also be used at the neural and activity levels of the ICF (Table 2). The neural level falls under both the health condition and the body structure categories in the ICF. Recovery at this level is limited because the lesioned area in the brain will not be able to return to the premorbid pattern of activity due to cell death (Levin et al., 2009). Restitution or repair will be strictly limited to the area surrounding the lesion and other distant areas that might have been left functionally damaged but can recover their activity over time (Buma, Kwakkel, & Ramsey, 2013). Compensation at the neural level is evidenced by patterns of activation that are not typically involved in performing a task in a healthy individual.

Table 2. Recovery and compensation at the different levels of functioning.

ICF Level	Recovery	Compensation
Health condition and Body structure (neuronal level)	Restoring function in neural tissue that was initially lost after injury.	Neural tissue acquires a function that it did not have prior to injury.
Body function (motor function)	Restoring the ability to perform a movement in the same manner as it was performed before injury.	Performing an old movement in a new manner.
Activity (functional use of the upper extremity)	Successful task accomplishment using extremities or end effectors typically used by nondisabled individuals.	Successful task accomplishment using alternate extremities or end effectors.

Definitions for recovery and compensation regarding the health condition, body structure and function, and activity. Adapted from Levin et al., 2009.

Regarding the activity level, recovery means performing a task in the same way as a healthy individual would do (Levin et al., 2009). For instance, in a right-handed stroke patient with right side paresis, recovery can be evidenced if the patient uses the affected extremity to pick up the phone. Compensation at this level would be using the unaffected extremity or making use of assistive devices. Importantly, recovery at the movement level is a necessary condition for

recovery at the activity level but not a sufficient cause. To consider that a patient shows recovery when doing a task, the pattern of movements should be what is considered normal. However, a patient with a good recovery at the motor level might still use compensatory strategies when performing a task. For instance, the patient may use assistive devices or the unaffected hand because they feel more secure regardless of the fact that normal movements can be performed with the affected extremity.

Compensatory movements may start very early after the stroke, and are usually self-taught and improved with practice (Bailey, Klaesner, & Lang, 2015; Jones, 2017). In some situations, therapeutic interventions may encourage the use of compensatory strategies. In patients with severe motor deficits and poor prognosis, compensatory strategies may be trained to regain functionality regardless of how movements are performed (Cirstea & Levin, 2000; Levin et al., 2009; Thielman, Dean, & Gentile, 2004). That is because, in rehabilitation, the aim is to maximise functional motor ability, focusing on successful task completion. Very often the term *functional recovery* has been misused in the field of stroke rehabilitation, referring to any gain in autonomy without paying attention if compensation was responsible for these gains (Kwakkel et al., 2004). Nevertheless, compensation can have negative consequences at the muscle level, increasing pain, spasticity and reducing the range of joint motion. It can also lead to learned non-use of the paretic extremity (André, Didier, & Paysant, 2004). Moreover, avoiding movements with the affected extremity can result in a degradation of the motor cortical representation. Thus, devoting efforts to compensation may promote forms of maladaptive plasticity that hinder the potential for recovery. There is a limited time window for increased plasticity and thus, therapeutic interventions during the first months after the stroke should focus on reducing the impairment rather than learning to compensate (Krakauer et al., 2012).

1.2.3 Mechanisms of neural plasticity

The nervous system is capable of changing its structure, connections and functions in response to intrinsic and extrinsic stimuli (Cramer et al., 2011). After a stroke, a sequence of mechanisms at the molecular, cellular, and synaptic level will promote endogenous plasticity in response to internally generated stimuli. The brain is also sensitive to external stimuli, and forms of experience-dependent plasticity will appear in response to demanding and enriched environments (Hyllin, Kerr, & Holden, 2017). The rehabilitation process aims to facilitate adaptive learning to promote brain reorganisation after stroke and boost the spontaneous mechanisms that the nervous system has to achieve functional recovery. Understanding the pattern of hemispheric reorganisation and the changes at a system level after injury is crucial to design therapeutic interventions that positively influence neural plasticity.

1.2.3.1 Hemispheric reorganisation

After cell death caused by a disruption of blood supply, the area surrounding the lesion and the non-lesioned hemisphere experience a series of functional and structural changes that may subserve the pattern of spontaneous recovery. Behavioural improvements depend on the ability of intact brain regions to support functioning. This ability is hindered by a cascade of cellular events after the stroke that includes reduction of blood perfusion, inflammation, edema and diaschisis (Figure 5).

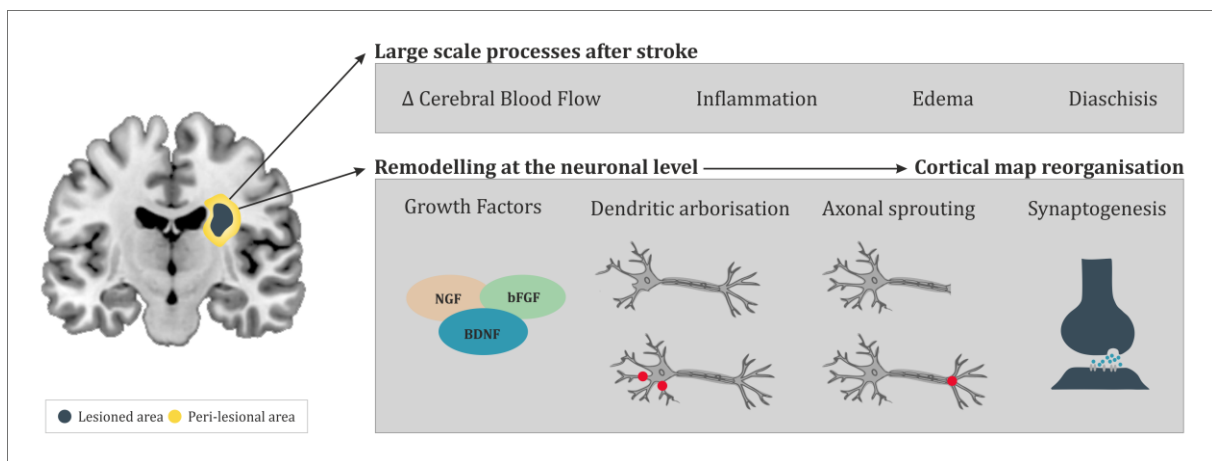


Figure 5. Large scale processes and remodelling at the neuronal level after stroke.

Large scale processes after stroke include changes in cerebral blood flow, inflammation, edema and diaschisis. The reduction or alleviation of these processes is responsible for initial spontaneous biological recovery. Moreover, there is a period of increased plasticity, where growth factors such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF), and brain-derived neurotrophic factor (BDNF) induce dendritic arborisation, axonal sprouting and synaptogenesis that lead to cortical map reorganisation. Adapted from Dalise, Ambrosio, & Modo, 2014.

The peri-lesional area, also known as peri-infarct or penumbra, shows reduced activity during the initial days after stroke. Neurons in this region become hypoexcitable mainly due to a failure in the re-uptake of the primary inhibitory neurotransmitter in the brain, GABA, by reactive astrocytes (Clarkson, Huang, MacIsaac, Mody, & Carmichael, 2010). The cessation of activity in the injured region and the functional decrease in the peri-lesional area disrupt the interhemispheric balance, and the non-lesioned hemisphere increases its activity (Duque et al., 2005; Murase, Duque, Mazzocchio, & Cohen, 2004). As the inflammatory processes decrease and blood reperfusion takes place, there is a phase of increased endogenous plasticity within the peri-lesional area in the first weeks post-stroke (Krakauer et al., 2012). This mechanism of endogenous plasticity is critical for recovery. After several days, neurons in the peri-lesional area become hyperexcitable and sequential waves of expression of growth-promoting genes are induced (Carmichael et al., 2005; Schiene et al., 1996). Changes in gene and protein expression promote the remodelling of dendritic spine architecture and axonal sprouting, which result in

the establishment of new connections (Figure 5, Carmichael, 2006; Carmichael et al., 2001; Dancause & Nudo, 2011; Stroemer, Kent, & Hulsebosch, 1995). These processes enable the reorganisation of topographic representations, with shifts and enlargement of cortical maps.

In 1949, Glees and Cole showed for the first time that after a focal lesion in the primary motor cortex in rhesus monkeys, the thumb representation was displaced and appeared in the adjacent region given time (Glees & Cole, 1949). Fifty years later, Nudo and colleagues (1996) observed similar changes with the distal forelimb representation in squirrel monkeys after a cortical stroke (Nudo, Wise, SiFuentes, & Milliken, 1996). In their study, monkeys had been previously trained in a task to retrieve food pellets from small wells that involved fine movements. Intracortical microstimulation was used to map the representation of hand movements in the animals before and after the injury (Figure 6A). After provoking a cortical stroke, monkeys showed motor limitations in the trained task as well as motor impairment in skilled wrist and hand movements, which were accompanied by a loss of cortical hand representation (Figure 6B). After the lesion, the animals underwent an intensive behavioural retraining of the food retrieval task. Notably, motor training induced not only behavioural improvements but also the distal forelimb representation was remapped, with expansions to the elbow and shoulder area (Figure 6D, Nudo et al., 1996). However, animals that did not undergo rehabilitative training showed a reduction in the distal forelimb representation (Figure 6C, Nudo & Milliken, 1996). Thus, training was crucial for the reorganisation of the lesioned hemisphere.

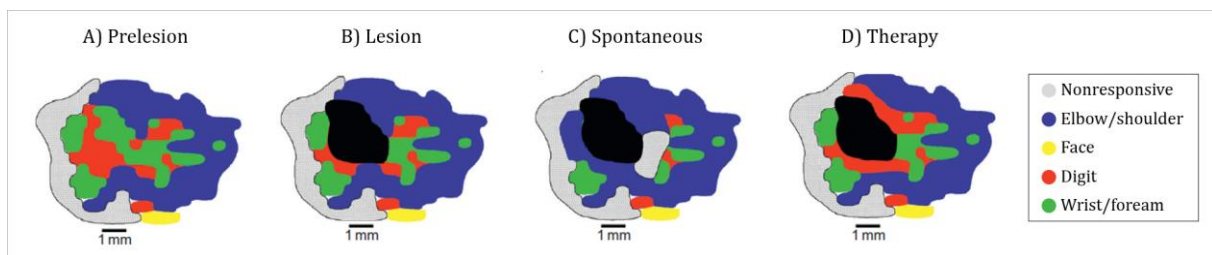


Figure 6. Reorganisation of the primary motor cortex in rhesus monkeys.

A) Cortical mapping of the primary motor cortex in rhesus monkeys. B) Focal ischaemic lesion (in black) provoked in the distal forelimb area. C) Spontaneous reorganization in animals that did not undergo training after the lesion. The distal forelimb representation is lost after the lesion. D) In animals that underwent motor training after the lesion, the loss of the distal forelimb representation is prevented and even increases its size in the peri-lesional tissue, expanding to areas that previously represented the elbow and shoulder. Adapted from Dancause & Nudo, 2011.

In the initial neuroimaging studies with humans in the nineties', an increase in regional cerebral blood flow and activity in the primary motor areas of the non-lesioned hemisphere was associated with recovery of the upper limb paresis (Chollet et al., 1991; Cramer et al., 1997; Willer, Ramsay, Wise, Friston, & Frackwiak, 1993). Thus, motor recovery was accompanied by a pattern of interhemispheric reorganisation. This finding would support the idea of a vicarious

model, where the unaffected hemisphere can take over the motor function of the ipsilateral paretic arm (Figure 7).

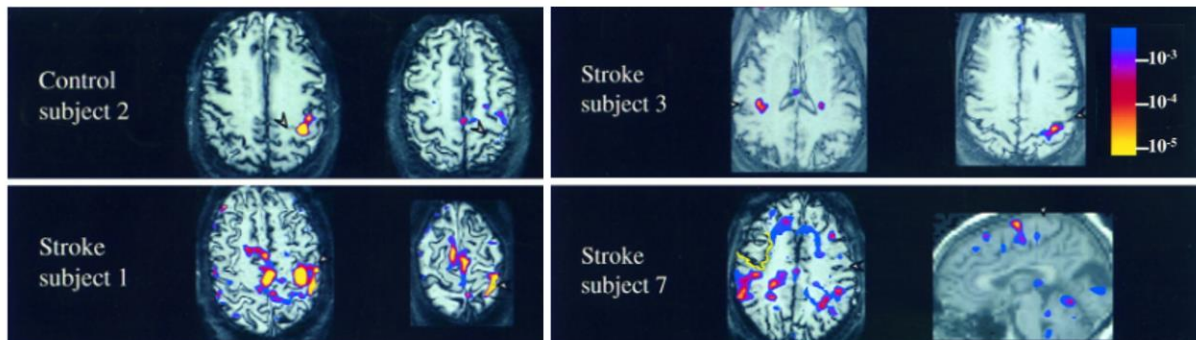


Figure 7. Example of interhemispheric reorganisation.

In control participants, contralateral activations are associated with unilateral hand movements. In stroke patients, bilateral activations were observed during movements with the paretic extremity. Adapted from Cramer et al., 1997.

In 1997, Netz and colleagues designed an impressive study to investigate the contribution of ipsilateral projections in the recovery of motor deficits after stroke using Transcranial Magnetic Stimulation (Netz, Lammers, & Hömberg, 1997). They evaluated chronic stroke patients and healthy participants, recording the electromyographic responses of the thenar muscle after cortical stimulation. In healthy individuals, cortical stimulation in the motor cortex is followed by contralateral muscle activity and inhibitory responses in the ipsilateral side (Figure 8A). In the group of stroke patients, they observed that those patients with poor recovery showed ipsilateral excitatory muscle activity in response to pulses over the unaffected hemisphere (Figure 8B). This means that movements of the paretic hand were elicited when stimulating the unaffected hemisphere. In contrast, controls and well-recovered patients showed contralateral muscle activity after stimulation, and ipsilateral excitatory responses were rarely observed.

The differences between patients with good and poor recovery led the authors to conclude that *“ipsilateral pathways seem to be of little significance for recovery, as the existence of these responses was not correlated with clinical improvement”* (Netz et al., 1997). Although reorganisation occurred in the non-lesioned hemisphere, it was not associated with motor recovery. The authors of this study argued that these ipsilateral responses in poor recovered patients might be due to disinhibition of a normally suppressed pathway rather than a plastic mechanism to compensate the motor deficit. Therefore the question arose: is the reorganisation of the affected hemisphere critical for recovery?

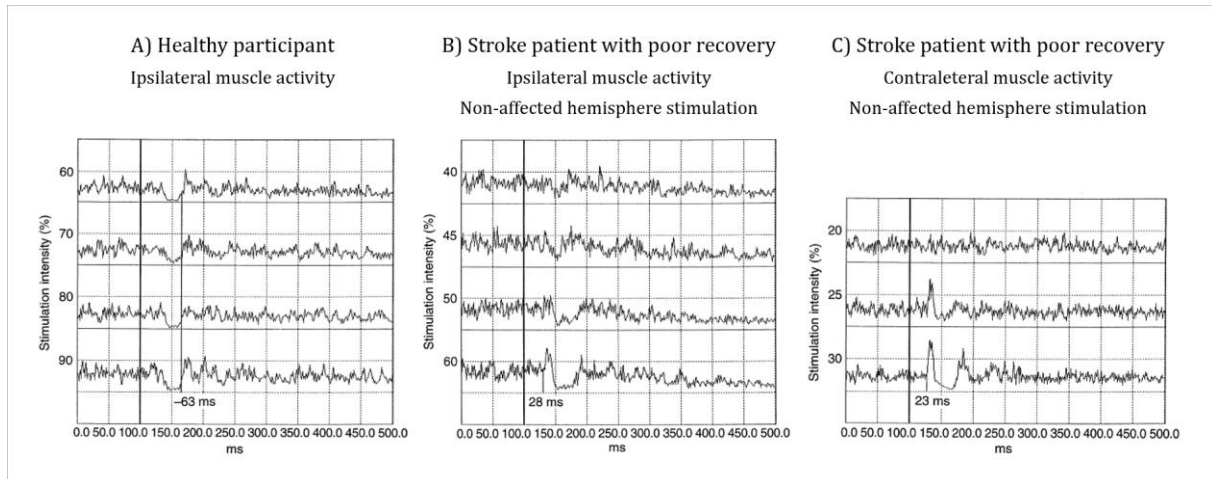


Figure 8. Electromyographic responses after cortical stimulation.

Electromyographic responses showing muscle activity of the thenar muscle in a healthy participant and a stroke patient with poor motor recovery after cortical stimulation with Transcranial Magnetic Stimulation. The stimulus onset is at 100 ms. A) In the healthy participant, a silent period is observed, showing inhibitory activity, in the muscle ipsilateral to the stimulated hemisphere. B and C) In the stroke patient, when the unaffected hemisphere is stimulated, motor-evoked potentials can be observed in the ipsilateral (paretic extremity) and contralateral muscles. Adapted from Netz et al., 1997.

Studies focusing on the excitability of the affected hemisphere over time in subacute stroke patients might offer an answer to this question. After the injury, motor-evoked potentials (MEPs) following stimulation of the affected hemisphere might be absent or reduced, which is in agreement with the initial period of hypoexcitability in the peri-lesional area observed in animal models. With time, MEPs can reappear or increase in size to abnormal levels. Traversa and colleagues (1998) found that after injury, the lesioned hemisphere shows increased excitability that is reduced over time (Traversa, Cicinelli, Pasqualetti, Filippi, & Rossini, 1998; Traversa, Cicinelli, Bassi, Rossini, & Bernardi, 1997). These findings are in line with the observation that neurons in the peri-lesional area became hyperexcitable days after injury in animal models (Schiene et al., 1996). With training, stroke patients can exhibit changes in excitability and reorganisation of cortical maps in primary motor areas and the somatosensory cortex of the lesioned hemisphere, which are associated with recovery (Carey et al., 2002; Johansen-Berg, Dawes, et al., 2002; Liepert et al., 1998). Specifically, cortical motor maps might be displaced to posterior or anterior regions of the affected motor cortex such as the somatosensory cortex, the premotor cortex or the supplementary motor area (Figure 9).

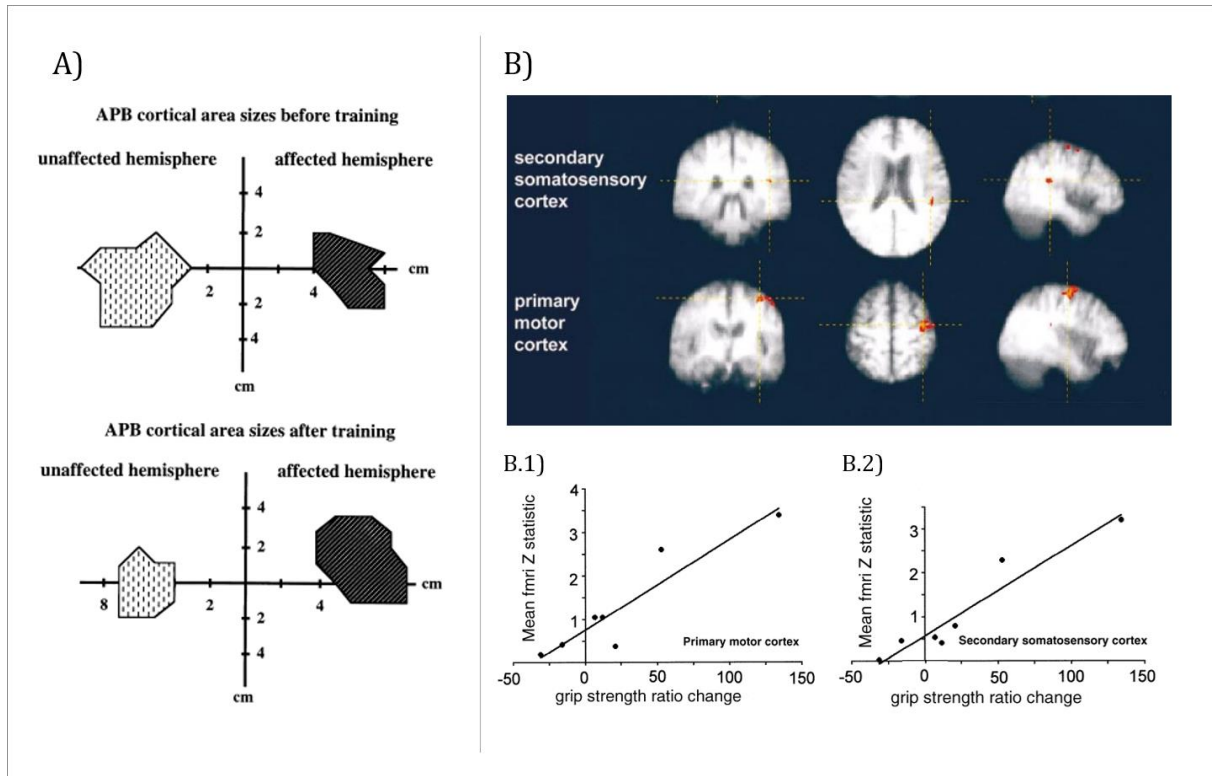


Figure 9. Examples of intrahemispheric reorganisation.

A) Cortical representation of the abductor pollicis brevis muscle (APB) before and after training with Constraint-induced movement therapy. Before training, the representation of the paretic muscle in the affected hemisphere was reduced and increased its size after training. Adapted from Liepert et al., 1998. B) Changes in activation when moving the paretic extremity after training. Reorganisation occurred in the somatosensory and the primary motor cortices of the lesioned hemisphere, which correlated with improvements in grip strength (B.1. somatosensory cortex, B.2. primary motor cortex). Adapted from Johansen-Berg et al., 2003.

In stroke patients, the non-lesioned hemisphere does not receive sufficient inhibitory inputs from the lesioned hemisphere after injury. This leads to an increase in excitability in the contralesional hemisphere, which exerts a greater inhibition on the lesioned hemisphere (Murase et al., 2004). The affected hemisphere is therefore doubly damaged, first by the injury and then by an excess of inhibition from the non-lesioned hemisphere (Di Pino et al., 2014). The return to a more normal pattern of brain activations in the lesioned hemisphere and the reduction of contralesional activity has been associated with good recovery (Carey et al., 2006; Cramer, 2008; Jaillard et al., 2005; Ward, Brown, Thompson, & Frackowiak, 2003b). In contrast, patients with poor recovery show increased bilateral activity and more substantial recruitment of contralesional areas (Cramer & Crafton, 2006; Grefkes et al., 2008; Teasell, Bayona, & Bitensky, 2005; Ward et al., 2003b). This indicates that intrahemispheric reorganisation would be more adaptive than reorganisation in the contralesional hemisphere and supports the idea of an interhemispheric competition model (Duque et al., 2005; Teasell et al., 2005).

Chapter 1. General introduction

As previously described, two models of hemispheric reorganisation exist and are opposed: the vicarious model, in favour of the unaffected hemisphere supporting ipsilateral motor function, and the interhemispheric competition model, which states that reorganisation within the affected hemisphere would be more adaptive. Di’Pino and colleagues (2014) have proposed that the gain of one model or the other would depend on the individual’s structural reserve to support function, in a model that was called the bimodal balance-recovery model (Di Pino et al., 2014). In the case of the motor system, structural reserve would be the remaining motor areas and the integrity of the corticospinal tract. If structural reserve is high, recovery will be associated with reorganisation within the lesioned hemisphere. In patients with severe damage to the motor pathways, reorganisation in the non-lesioned hemisphere would better predict recovery (Figure 10). Thus, the anatomical damage would determine if restitution can occur in the lesioned hemisphere.

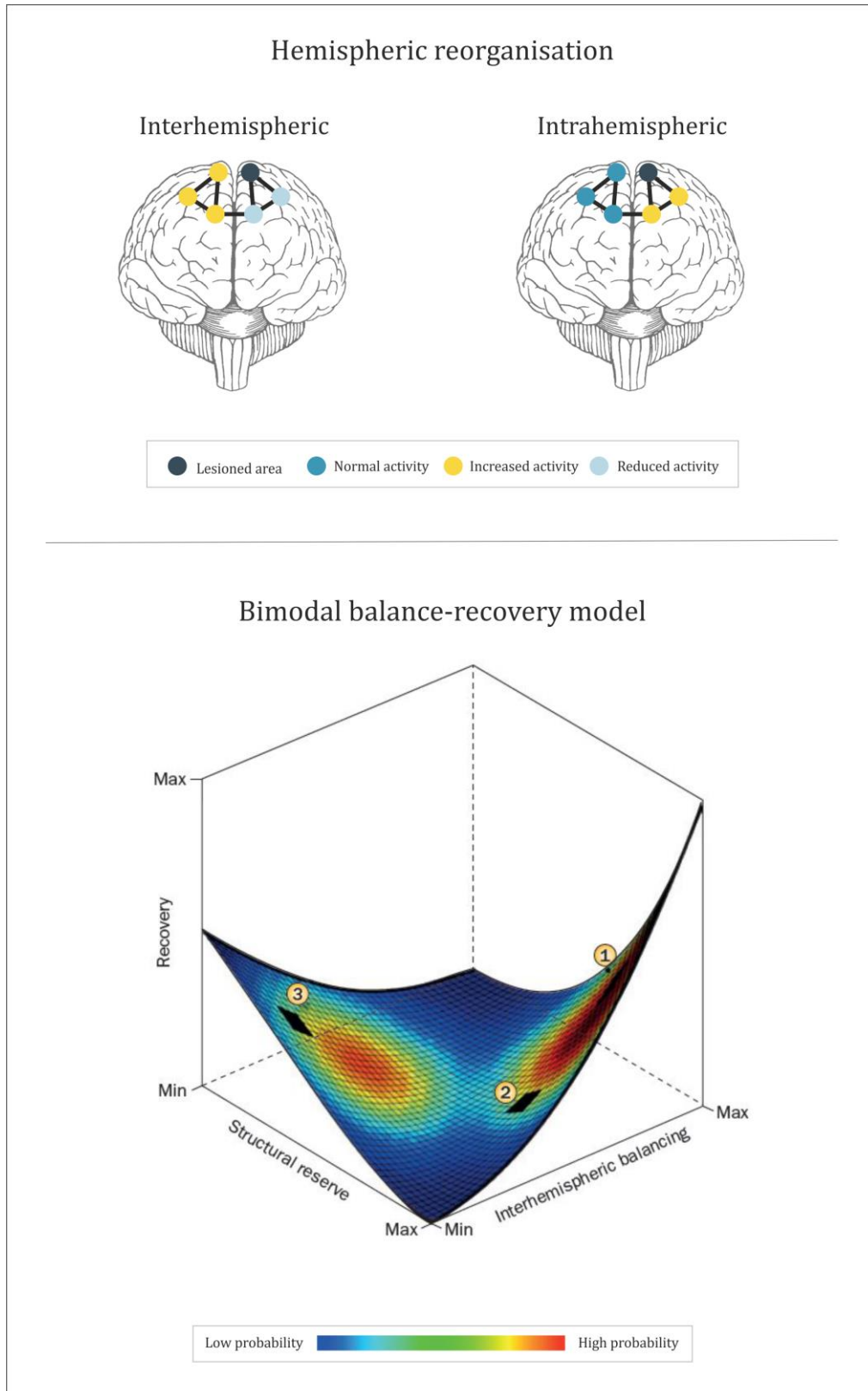


Figure 10. The bimodal balance-recovery model.

Interhemispheric balancing, and thus the pattern of hemispheric reorganisation, depends on the amount of structural reserve. If structural reserve is high, there is a high probability of reorganisation in the affected hemisphere. If structural reserve is low, there is a high probability of reorganisation in the non-affected hemisphere. Numbers 1, 2 and 3 represent different scenarios of recovery taking into account structural reserve and interhemispheric balancing. Adapted from Di Pino et al., 2014.

These two types of reorganisation differ in their use of the remaining neural reserve. In the affected hemisphere, the premotor cortex may increase its connections with the remaining corticospinal tract or use alternative motor pathways such as the reticulospinal pathway to control proximal upper extremity muscles (Baker, 2011). The reorganisation in the non-lesioned hemisphere depends on the uncrossed fibres of the corticospinal tract (around 15%) to support ipsilateral motor function (Alawieh, Tomlinson, Adkins, Kautz, & Feng, 2017). The reasons behind why reorganisation within the affected hemisphere correlates with better behavioural outcomes might be that i) the amount of structural reserve is higher and ii) the neural pathways used may be more efficient (Di Pino et al., 2014). There are numerous plastic mechanisms at the system level that operate in parallel and underlie hemispheric reorganisation. These mechanisms can support (i.e. structural reserve) or impede correct functioning.

1.2.3.2 Mechanisms of adaptive and maladaptive plasticity

At the system level, plastic changes can be adaptive when reorganisation results in a gain in function, or maladaptive when the function is altered or lost (Fornito, Zalesky, & Breakspear, 2015). Mechanisms of adaptive plasticity are compensation, neural reserve and degeneracy. Maladaptive responses to injury include diaschisis, dedifferentiation and transneuronal degeneration (Figure 11).

The principal mechanism that supports the maintenance of a function after an insult is compensation. Compensation at the neural level is the involvement of undamaged regions in carrying out a function from a damaged area (Figure 11, Bernhardt, Hayward, et al., 2017). It is expressed as an increase in activation or functional connectivity that preserves the function to varying degrees. The area surrounding the lesion and distant regions within the same neural system, including regions in the non-lesioned hemisphere, can be activated to support function (Johansen-Berg, Rushworth, et al., 2002; Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012; Riecker et al., 2010). Compensation is viewed as an adaptive mechanism only when it is accompanied by successful behaviour, which will depend on the amount of neural reserve and degeneracy of systems (Jaillard et al., 2005).

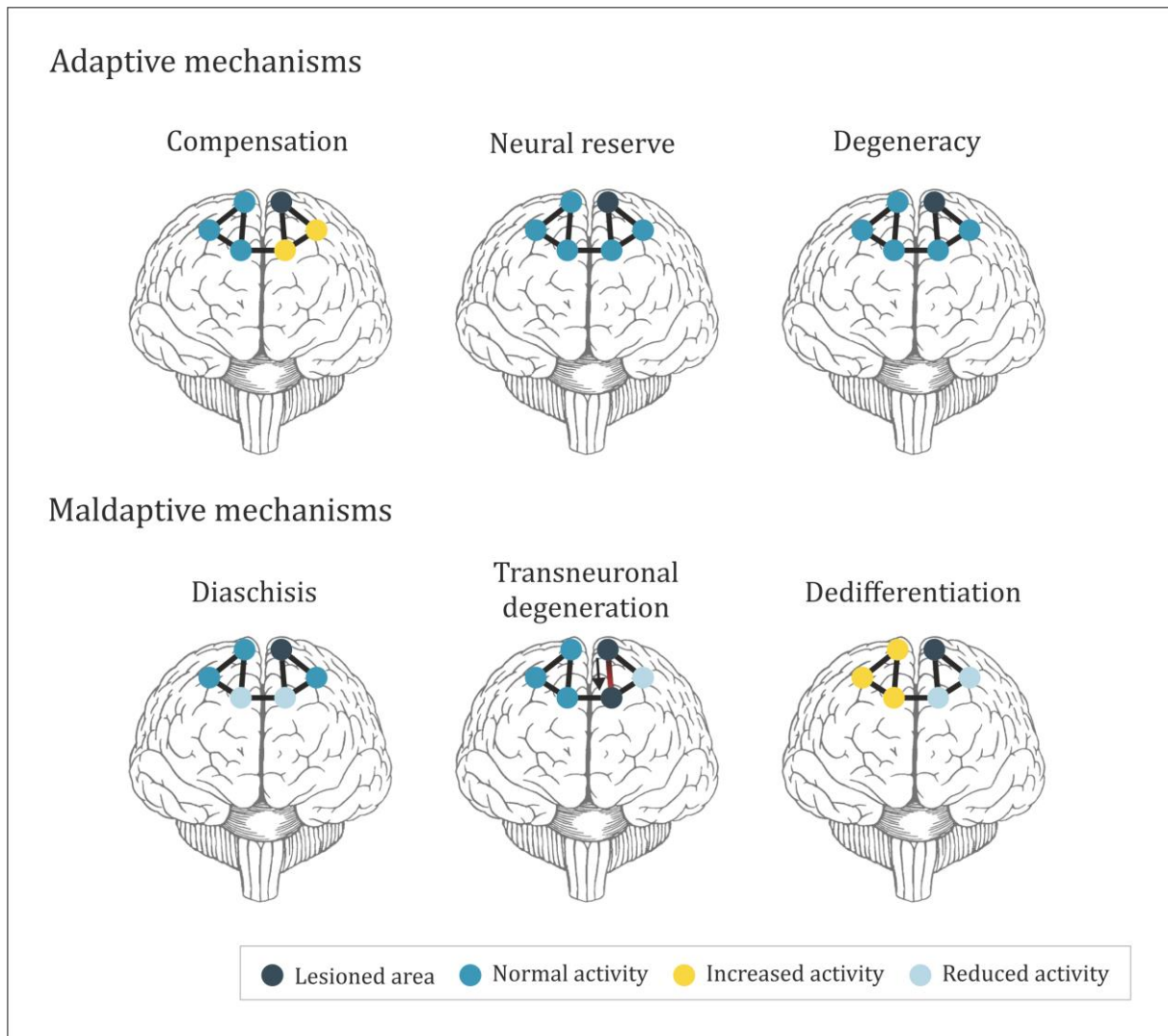


Figure 11. Adaptive and maladaptive plastic mechanisms at the network level.

Adaptive mechanisms are compensation, neural reserve and degeneracy. In compensation, unaffected regions increase their activity to support function. In neural reserve, the activity of other regions is not needed because the network is still able to sustain function. Degeneracy refers to a second system supporting function but without interfering with the normal functioning of this second system. Maladaptive mechanisms are diaschisis, transneuronal degeneration and dedifferentiation. Diaschisis is a dysfunction in regions distant from the lesion. Transneuronal degeneration is the degeneration of remote regions with time. Dedifferentiation refers to the activation of other networks that are non-specialised to sustain a particular function. Adapted from Fornito et al., 2015.

Neural reserve as a mechanism of plasticity refers to the structure and integrity of the nervous system as well as its efficient use in the performance of a task (Steffener & Stern, 2012; Stern, 2002). Structural or brain reserve can be quantified as grey matter density, cortical thickness, or white matter integrity. In stroke patients, the integrity of the corticospinal tract is an important predictor of recovery (Stinear, 2010). The balance between the number of damaged areas and the remaining neural substrate can determine if a function will be sustained, regained with time or lost. Moreover, if the remaining neural tissue shows high degeneracy, also known as redundancy or vicarious function, it would support behaviour (Figure 11, Fornito et al., 2015).

Cognitive reserve is the use of this structural reserve in its more efficient and flexible manner. While performing a task, highly efficient neural networks make use of fewer resources but when demands of the task increase, these networks can reach their maximum capacity (Steffener & Stern, 2012). Thus, individuals with high cognitive reserve show a pattern of less brain activation in performing tasks and greater activations if the task becomes too demanding. The integrity and specialisation of connections and neural systems are mainly shaped during development, but they are also influenced by experience during our lifespan. Level of education, intelligence quotient, mental activity, occupational complexity, participation in leisure activities and social interactions have been shown to be modulators of cognitive reserve (Kelly et al., 2017; Richards & Sacker, 2010; Staff, Murray, Deary, & Whalley, 2004; Verghese et al., 2003). Thus, the variability in brain and cognitive reserve across individuals may play an essential role in understanding individual differences in response to injury.

Regarding maladaptive mechanisms, diaschisis might be the most studied phenomenon in this category. Diaschisis was first described by von Monakow in 1914 as the interruption of function in regions that are distant to a focal injury (Figure 11, Finger, Koehler, & Jagella, 2004). A hundred years later, Carrera and Tononi refined the term as distant neurophysiological changes provoked by a focal injury (Carrera & Tononi, 2014). Neurophysiological changes include reduced or altered metabolism, cerebral blood flow and neural activity, which are responsible for clinical manifestations that tend to normalise with time. Diaschisis alters distributed neural dynamics and is system-selective; thus only remote regions within the same neural system can be affected (Nomura et al., 2010).

Functional alterations by diaschisis can manifest in a specific brain region (*focal diaschisis*) or in a diffuse manner (*connectional diaschisis*). Focal diaschisis can be observed at rest as a reduction of metabolic function in an intact distant area (Baron et al., 1984). For instance, glucose metabolism is reduced in distant cortical regions following small cortical strokes as evidenced in animal models (Carmichael, Tatsukawa, Katsman, Tsuyuguchi, & Kornblum, 2004). Using magnetic resonance imaging spectroscopy, Craciunas and colleagues (2013) observed a reduction of metabolism in the ipsilesional primary motor cortex, dorsal premotor cortex and supplementary motor area that was negatively correlated with motor deficits of the upper extremity in patients with subcortical stroke (Craciunas et al., 2013). Nevertheless, it may be possible that a region with normal metabolism or blood flow at rest shows altered neural activity only during stimulation or activation of the neural system, which is known as functional diaschisis (Di Piero, Chollet, Dolan, Thomas, & Frackowiak, 1990; Ginsberg, Castella, Dietrich, Watson, & Busto, 1989). As previously described, after a cortical lesion in the motor cortex, the contralesional hemisphere can show overactivation during movements of the impaired

extremity, together with reduced metabolism and augmented somatosensory evoked potentials (Cirstea et al., 2014; Cramer, Finklestein, Schaechter, Bush, & Rosen, 1999; Mohajerani, Aminoltejari, & Murphy, 2011). The involvement of the contralesional hemisphere in ipsilateral movements can be identified as dedifferentiation if there is sufficient neural reserve in the affected hemisphere to support contralateral motor function.

Connectional diaschisis is the alteration of inter-regional synchronisation, when the functional coupling between two regions is reduced (Campo et al., 2012). Connectivity alterations are evidenced in studies using functional and effective connectivity analysis. For instance, stroke patients can present a reduction in connectivity from the superior parietal cortex to the supplementary motor area and primary motor cortex, reflecting alterations in top-down processes of motor control (Inman et al., 2012; Zhao et al., 2016). The reduction in connectivity can affect specific networks but also the structural connectome.

If diaschisis is a functional alteration in distant regions, transneuronal degeneration is a structural deterioration in areas remote to the injury (Figure 11). Although diaschisis tends to resolve with time, functional dedifferentiation sustained in time can provoke structural damage in the long term. At the cellular level, transneuronal degeneration can affect both the presynaptic and postsynaptic neurons due to lack of trophic support or excitatory or inhibitory inputs. Degeneration can manifest as a decrease in myelin and dendrite number and can lead to cell death (Fornito et al., 2015). After a cortical stroke, the reduction in projections from the cortex to the thalamus can be accompanied by degeneration of the thalamus, with reductions in its size and increase of glial cells in a rat barrel model (Carmichael et al., 2001). In humans, transneuronal degeneration has been well characterised in neurodegenerative diseases. In stroke patients, Diffusion Tensor Imaging studies have provided new insights about the Wallerian degeneration of the corticospinal tract (Thomalla et al., 2004; Werring et al., 2000) that correlate with the extent of motor deficits (Puig et al., 2017) and is associated with recovery prognosis (Stinear, 2010; Yu et al., 2009).

1.2.4 Time window of stroke recovery

The different phases of stroke recovery are based on the time course of plastic mechanisms and spontaneous biological recovery. Recently, Bernhardt and colleagues (2017) proposed a consensus framework that classifies stroke recovery phases in hyper-acute, acute, early and late subacute, and chronic (Figure 12, Bernhardt, Hayward, et al., 2017).

The first 24 hours after the stroke are characterised at the cellular level by cell death and haematoma expansion in the case of haemorrhagic strokes. The available vascular treatments to

save neural tissue through reperfusion are limited to a narrow time window up to 4.5 hours after the stroke onset (Hacke et al., 2008; Lansberg, Bluhmki, & Thijs, 2009). Glial activity, which commences very early after the insult, reaches its peak the first days after the stroke. The failure in the regulation of GABA neurotransmitter by reactive astrocytes and the reduction of blood supply leave the peri-lesional area with decreased activity (Clarkson & Carmichael, 2009). Moreover, regions distant to the lesion might show altered metabolism and functioning (Carmichael et al., 2004). During the first days post-stroke, improvements at the functional level can be observed as a result of blood reperfusion in the penumbra, reduction of inflammatory processes and resolution of diaschisis (Kwakkel et al., 2004).

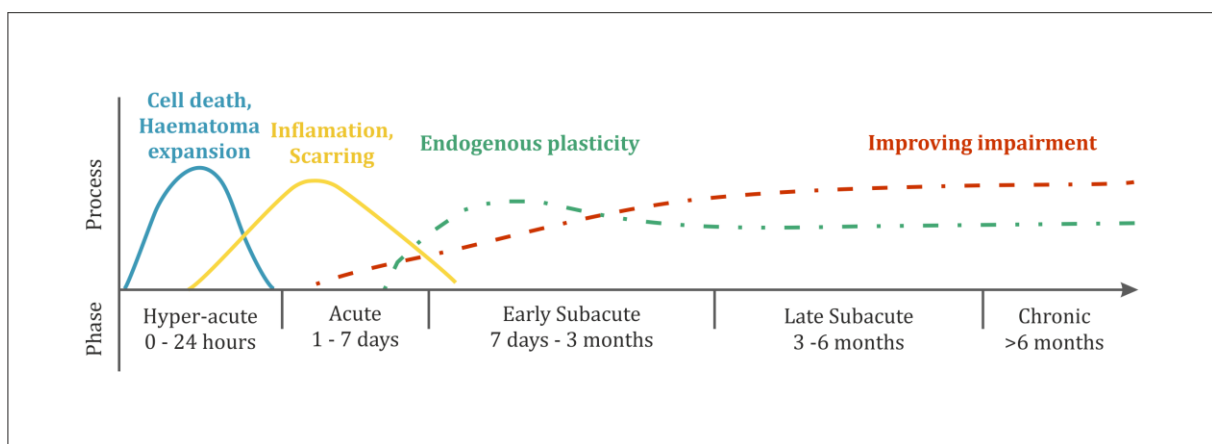


Figure 12. Phases of stroke recovery and neural processes.

Stroke recovery phases are hyper-acute, acute, early and late subacute, and chronic. The main cellular processes are cell death, haematoma expansion (this latter only in the case of haemorrhagic strokes), inflammation and scarring, which peak in the initial hours and days after the lesion and decrease rapidly. These processes are followed by a period of increased endogenous plasticity that supports behavioural improvements. Adapted from Bernhardt, Hayward, et al., 2017.

The early subacute phase is a period of increased plasticity where the potential for recovery is maximum (Krakauer et al., 2012). In animal models, it has been shown that if training is not provided or starts later than a month after the injury, the reorganisation of cortical maps does not occur (Biernaskie, 2004). These findings reveal that the period of increased plasticity is time limited. In humans, this period can extend up to ten weeks. Endogenous plastic mechanisms begin to plateau at three months, and most of the possible motor recovery will be achieved during this period (Kwakkel et al., 2004).

With improvements in body functions reaching a plateau, the late subacute phase is defined by functional improvement at the activity and participation level, which is achieved through mechanisms of adaptive and substitutive compensation (Jones, 2017). A stabilisation of deficits characterises the chronic phase. However, numerous studies have found that functionality can be improved with training in chronic stroke patients (Bang, Shin, & Choi, 2015; Michielsen et al.,

2011; Page, Murray, Hermann, & Levine, 2011). Of much debate is that if these findings are evidence of compensation rather than a reduction in impairment since neural restoration is unlikely to occur (Zeiler & Krakauer, 2013). A multicentre study found that patients experience a deterioration five years after the stroke, showing the same functional level they had at two months post-stroke (Meyer et al., 2015). It could be that after experiencing a decrease in functionality, training in the chronic phase may lead to the same level of functionality as achieved at the end of the rehabilitation process. In any case, exercising and carrying out active and stimulating activities in the chronic stage should be encouraged to maintain an optimal level of activity after discharge and prevent patients from declines in functionality (Winstein et al., 2016).

On the whole, the consensus on the existence of these phases, which are based on the timing of biological processes and are informed by the most recent evidence from animal studies, should be considered when determining the optimal phase for specific interventions (Bernhardt, Hayward, et al., 2017).

1.2.5 Promoting plasticity through experience

Two main ideas arise from the evidence on the plastic mechanisms after stroke and their time course. Firstly, spontaneous neurological recovery after the injury is mainly explained by reperfusion of blood in the penumbra, reduction of inflammatory processes and edema, and alleviation of diaschisis (Kwakkel et al., 2004). Secondly, there is a period of increased plasticity that is limited in time and may create a favourable environment for the establishment of new connections (Krakauer et al., 2012). This favourable environment, with increased expression of growth-promoting factors such as brain-derived neurotrophic factor (BDNF), would make the nervous system more sensitive to forms of experience-dependent plasticity (Buma et al., 2013). How these elements interact together with the training process entails high complexity (Figure 13).

On the one hand, spontaneous biological recovery is driven by the recovery of penumbral tissue, reduction of inflammation and alleviation of diaschisis but also by homeostatic mechanisms that allow a period of increased plasticity (Buma et al., 2013; Kwakkel et al., 2004). Even in the absence of treatment, spontaneous biological recovery can lead to the reorganisation of cortical maps, affecting the brain's ability to perceive and modulate responses in a manner that it does not depend on experience or learning mechanisms. On the other hand, the period of increased plasticity that is extended up to three months creates a favourable environment for enhancing forms of experience-dependent plasticity (Krakauer et al., 2012). Motor skill acquisition,

therefore, is subserved by spontaneous biological recovery and experience-dependent plasticity. Both types of plasticity will lead to the reorganisation of cortical maps. This map reorganisation constitutes the neural substrate to enhance body functions through recovery or compensation, influencing adaptive motor control and improving task performance.

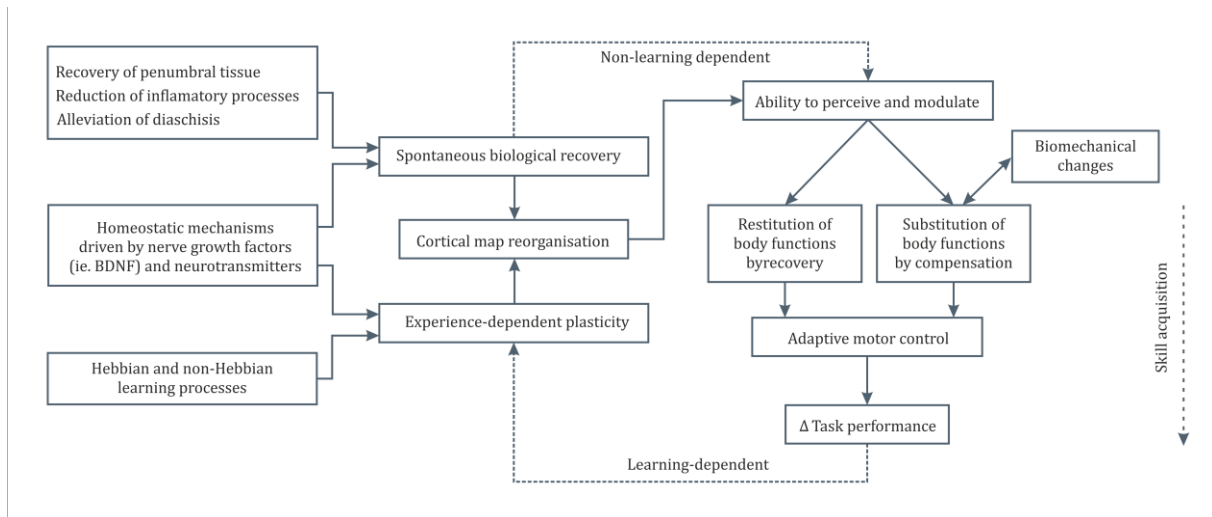


Figure 13. Model of interactions between distinct crucial elements in stroke recovery.
Adapted from Buma et al., 2013.

One of the biggest challenges in the field of neurorehabilitation is to understand how to modulate the mechanisms of increased plasticity through therapeutic interventions. At the behavioural level, two main approaches arise to ameliorate motor deficits and induce forms of experience-dependent plasticity: training and enriched environment.

1.2.5.1 Training to promote motor skill acquisition

A well-accepted principle in stroke rehabilitation is that training should be task-specific. This means that training should aim to learn or relearn a specific skill through practice (Carr & Sheperd, 1987, 1990). In task-specific training, learning is oriented to achieve functionality in a particular activity or a set of tasks that are relevant for everyday life activities (Van Peppen et al., 2004). Thus, training should be explicit and goal-directed. Most of the available treatments to restore motor deficits after stroke fall under this approach, which can be combined with enriched environment (Pollock et al., 2014). Task-specific training aims to promote motor skill learning in stroke patients to achieve the acquisition, consolidation and long-term retention of motor patterns in a specific activity (Krakauer, 2006).

In healthy individuals, motor skill learning is the process by which movements are performed more quickly and accurately with practice (Willingham, 2001). Motor skill acquisition is initially

characterised by a fast learning phase where rapid improvements in movement velocity and accuracy occur together with reductions in reaction time and movement variability (Dayan & Cohen, 2011; Kami et al., 1995). As learning progresses, there is a slow-learning phase defined by a refinement of movement patterns. During this phase, improvements are less prominent, but movements become more automatic, with less need of attentional and executive processes (Doyon & Benali, 2005). The spacing between the training sessions constitute the off-line periods, where motor memory consolidation occurs, making the long-term retention of movement patterns possible. A network of cortical, subcortical and cerebellar regions experience functional and structural changes in response to motor training (Dayan & Cohen, 2011; Draganski et al., 2004). Theories of motor learning in healthy individuals might provide insights about the optimal conditions to facilitate effective learning and better motor performance in stroke patients (Kitago & Krakauer, 2013; Wulf & Lewthwaite, 2016). From these theories, some elements of the training should be considered to be incorporated into therapeutic interventions to enhance motor recovery:

Relevance of task: the task selected to be trained should have real-world relevance and is advised to be chosen by or in collaboration with the patient (Arya et al., 2012). When doing so, there is recognition of the needs of the patient as well as their motivation and enjoyment towards the therapeutic activity (Wressle, Eeg-Olofsson, Marcusson, & Henriksson, 2002).

Instructions and guidance: to facilitate the approximation to the desired motor behaviour in a given task, the therapist may provide direct instructions and guidance. Importantly, instructional language should be autonomy-supportive (Hooyman, Wulf, & Lewthwaite, 2014). This means that it should provide opportunities for choice in how to perform the task. Moreover, instructions should focus on the goal of the action instead of the required movements (Wulf & Lewthwaite, 2016). It has been shown that directing attention towards the goal leads to better performance whereas focusing on how movements are performed might constrain the motor system and interfere with automatic movement processes (Wulf, McNevin, & Shea, 2001; Wulf & Prinz, 2001). This is particularly tricky in the case of stroke rehabilitation since particular emphasis should be placed on avoiding compensatory movements (Krakauer et al., 2012). Furthermore, in the interaction with the patient, implying that abilities are malleable instead of fixed can increase self-efficacy and positive affect and therefore, impact learning (Jourden, Bandura, & Banfield, 1991; Wulf & Lewthwaite, 2009).

Prompting: cues can be used to prompt motor behaviour. The therapist should take into account if the patient is ready to initiate the desired performance and should progressively stop using prompts as the patient progresses.

Modelling: skill demonstration can be used to show how the task should be performed. The patient should imitate motor behaviour, which can be demonstrated by the therapist or making use of video recordings (including self-modelling of best trials).

Mass practice of movements: a component of motor learning is movement repetition. Mass practice of movements promotes use-dependent plasticity. However, this form of plasticity may not be enough to promote recovery at the motor level after stroke. It has been shown that repetition of movements alone does not induce cortical reorganisation (Plautz, Milliken, & Nudo, 2000). Mass repetition should be embedded in the context of motor learning to promote plastic changes. Thus, the existence of a goal-driven process, with active problem solving to respond to environmental demands, is crucial for motor recovery (Fu, Yu, Lu, & Zuo, 2012; Kitago & Krakauer, 2013). The amount of practice is a relevant component of learning, which is related to training intensity.

Reinforcement: providing a reinforcer in response to good trials or approximations to the desired performance can trigger a dopaminergic-mediated response that enhances motor learning (Wager & Atlas, 2015; Wulf & Lewthwaite, 2016). This can be explained because dopaminergic neurons, which play a crucial role in reward-based learning, have projections to the primary motor cortex (Awenowicz & Porter, 2002). Thus, reinforcers during motor skill learning can induce long-term retention of motor skills (Hosp & Luft, 2013; Hosp, Pekanovic, Rioult-Pedotti, & Luft, 2011; Thabit et al., 2011). Reinforcers in rehabilitation can be extrinsic, like feedback or getting points in a game competition environment, or intrinsic such as the feeling of success. Importantly, just the anticipation of the reward is sufficient to trigger the release of dopamine (Berridge, 2007). In regard to feedback, providing information about the performance of the patient particularly after a good trial reinforces successful performance and maximises learning (Chiviawsky & Wulf, 2007; Helmer et al., 2011; Saemi, Porter, Ghotbi-Varzaneh, Zarghami, & Maleki, 2012). Moreover, it has been shown that providing positive social comparative feedback increases the sense of competence, satisfaction, positive affect and motivation, and reduces concerns and nervousness towards the task (Lewthwaite & Wulf, 2010; Wulf & Lewthwaite, 2016). Negative feedback has been traditionally linked to degraded motor learning and performance. However, Galea and colleagues (2015) observed that negative feedback can lead to faster learning through aversive conditioning (Galea, Mallia, Rothwell, & Diedrichsen, 2015). Error-based motor learning is mediated by the cerebellum, which plays a crucial role in monitoring errors and encoding negative feedback associated with motor performance. Errors are necessary for learning, and either an excess or a lack of errors have a detrimental impact on learning. For instance, being aware of an excessive number of errors can lead to frustration and interfere with optimal learning (Wulf & Lewthwaite, 2016). On the

contrary, experimental settings that allow errorless performance have been shown to slow motor improvement during skill acquisition (Pomeroy et al., 2011).

Shaping and chaining: dividing the task or activity into multiple levels or steps serves to break down the requirements to approximate to the desired behaviour (Taub, Uswatte, & Elbert, 2002). Furthermore, this strategy can be useful in reducing the perceived task difficulty, making the task less daunting for the patient. Feedback and reinforcers can be provided after completing levels or steps.

Fading: as the desired performance is achieved gradually by shaping and chaining, the removal of cues, aids to perform the task or physical support should be done to promote autonomy in the task.

Autonomy: providing control over the practice may be inherently rewarding and can increase motivation (Eitam, Kennedy, & Higgins, 2013; Lewthwaite, Chiviacowsky, Drews, & Wulf, 2015). For instance, allowing the patient to decide the extent of the practice and the order of tasks, or when to rest, receive feedback or help can increase learning. Supporting autonomy in training has been shown and enhance motor learning through the up-regulation of BDNF production (Ploughman et al., 2005).

Most of the elements described have been incorporated in the OPTIMAL model of motor learning (Figure 14, Wulf & Lewthwaite, 2016). This model proposes an explanation of how motivational and attentional factors influence motor learning. On the basis that human behaviour, and specifically motor skill learning, occurs in contexts that have cultural and societal elements, the OPTIMAL model incorporates a perspective that takes into account how social, cognitive and affective factors affect motor learning. The authors of this model argue that motivation in motor behaviour is linked to expectations of success and the need to feel autonomous. On the one hand, expectancies can be described as predictive and anticipatory cognitions for future performance success. Motor learning can be facilitated in a training environment that enhances expectancies through positive feedback, positive affect, reward or perceived task difficulty, modulating perceptions of self-efficacy and outcome predictions. On the other hand, the need for autonomy plays an essential role in learning. Actively involving the individual in training and promoting their autonomy would improve perceptions of competence and sense of agency. Moreover, if the individual perceives themselves as an active agent in control of their environment, this will result in enhanced expectancies through self-efficacy beliefs (Wulf & Lewthwaite, 2016).

Regarding attentional processes, an external focus of attention in preparing or executing the movement has been shown to enhance motor learning and motor performance. Directing the attention to the outcome of the task might facilitate automaticity in movement responses and lead to forms of implicit learning. On the contrary, focusing on body movements leads to consciously control motor commands, which interferes with automatic and unconscious movement processes. Therefore, reducing self-focus and adopting an external focus towards the movement outcome has beneficial effects of movement effectiveness and efficiency, reinforcing motor learning (Wulf & Lewthwaite, 2016).

Motivation and attention are thought to enhance goal-action coupling, increase the focus on task goal and therefore improve motor performance and learning (Figure 14).

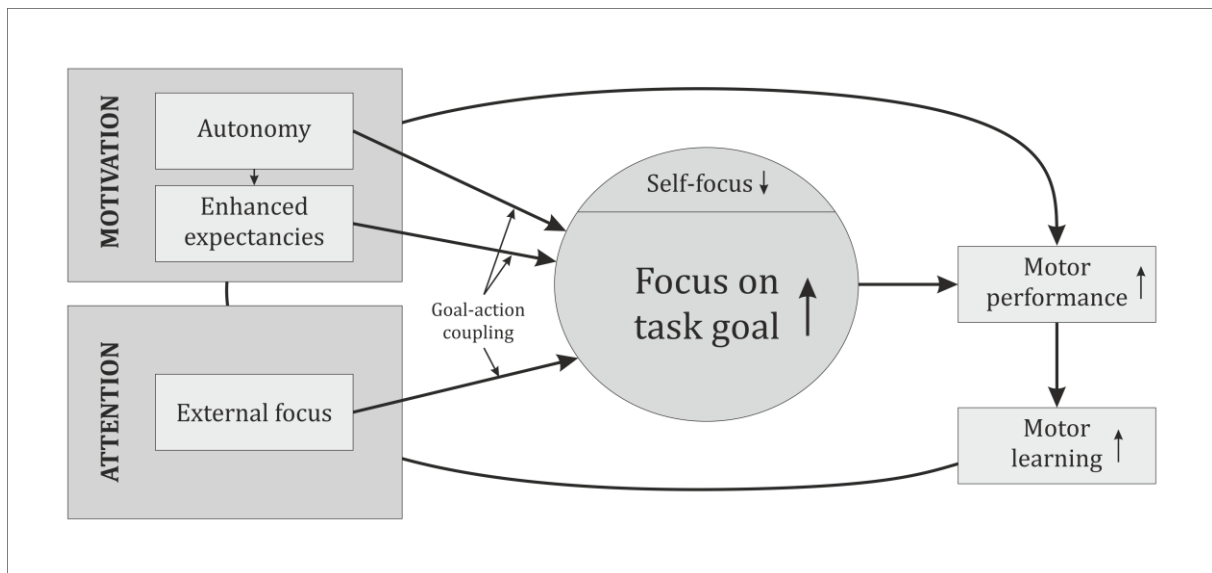


Figure 14. The OPTIMAL theory of motor learning.

Through modulating motivation and attention, goal-action coupling can be enhanced during motor training. This leads to focus on the task goal, which boosts motor performance and learning. Adapted from Wulf & Lewthwaite, 2016.

1.2.5.2 Enriched environment

Enriched environment refers to providing an interactive context that stimulates physical, cognitive and social activities, as well as multimodal sensory processing. Under the premise that the environment in which training occurs is critical, enriched environment enhances learning and recovery of the sensorimotor function (Janssen et al., 2010; Johansson, 1996; Johansson & Ohlsson, 1996). Moreover, enriched environment promotes plasticity after stroke, increasing neurogenesis, dendrite spine growth, synaptogenesis, and the production of neurotrophic factors (Biernaskie, 2004; Biernaskie & Corbett, 2001; Hicks et al., 2007; Komitova, Mattsson, Johansson, & Eriksson, 2005; Livingston-Thomas et al., 2016). Most of the research about the

benefits of enriched environment has been conducted in animal models, in which the housing conditions are manipulated with different tactile features, sensory equipment, and access to exercises together with novel and varied stimuli. The translation into a human equivalent would be multimodal stimulation (Pekna, Pekny, & Nilsson, 2012). Enriched environment in humans would require modifying the rehabilitation and home environment to make them stimulating and challenging (Mandolesi et al., 2017; Marcheschi, Von Koch, Pessah-Rasmussen, & Elf, 2018). Janssen and colleagues (2014) provided hospitalised stroke patients with communal and individual equipment and activities (Janssen et al., 2014). Computers, books and newspapers, music, word and number puzzles, and board games were available to patients, who were encouraged by staff and family members to engage in these activities in their free time at the hospital. Patients increased their level of activity and were less isolated (Janssen et al., 2014). It is estimated that more than 70% of the time in rehabilitation centres, stroke patients are inactive and alone in their rooms (De Wit et al., 2005). Enriched environments can engage patients in activities, having a positive influence on motivation and well-being, and can be easily combined with other treatments to boost motor recovery (Sommer & Schäbitz, 2017; White, Bartley, Janssen, Jordan, & Spratt, 2015)

1.2.6 Evidence-based therapies for motor deficits of the upper extremity

Several rehabilitative techniques aim to restore motor function after stroke, but their acceptance and implementation into clinical practice depend on the available evidence supporting their effectiveness.

1.2.6.1 Assessing evidence quality and treatment effectiveness

The levels of evidence in medicine establish a ranking system to differentiate sources of information and study designs, grading the certainty of treatment effectiveness regarding the quality of available evidence.

The foundational level of evidence is provided by expert opinions or editorials about why a therapy might work. These articles usually expose ideas or questions that arise from basic research or clinical practice and propose plausible explanations based on physiology for the effectiveness of a particular intervention. In a similar vein, uncontrolled case reports are a source of ideas and hypotheses for developing therapy techniques. To make valid inferences, single-case designs allow developing and testing therapeutic interventions in a unique way that is not feasible with a large number of participants. These designs are characterised by continuous assessment, with repeated observations of the patient's performance over time,

embedded in an experimental design that allows comparing different conditions. Individual case-control designs can be used to determine the benefits and harms of a therapy compared with no treatment or other interventions (Smith, 2012). Research questions at this stage are also related to the feasibility of the therapy, and whether it is viable to apply it, constituting a proof-of-concept for the implementation of a treatment (Iwakabe & Gazzola, 2009). Single-case studies are often used in medicine, psychology, social work or education and, despite the critic that their results cannot be generalised, these types of design are highly valuable for several reasons. First, single-case studies offer the possibility of investigating the effectiveness of a therapy and compared it to a control condition using an experimental design. Second, the participant serves as his own control. The within-subject nature of the design allows ruling out problems of individual differences when comparing two groups of participants. Third, the continuous collection of data serves as a basis to study the progression of the patient during the treatment or control condition.

If the therapy has been proved to have a beneficial effect and seems to be feasible, studies can be conducted with larger cohorts of patients. Between-groups designs aim to explore all the possible benefits and harms at a group level and select the most sensitive outcomes. Usually, relevant aspects of the therapy are manipulated to find the most appropriate protocol. If the results of these experimental studies seem promising, the next step would be to conduct randomised controlled trials (RCTs).

RCTs are the gold standard design in clinical research. This design is characterised by the use of a control group and the randomisation of patients into the experimental or the control group (Friedman, Furberg, DeMets, Reboussin, & Granger, 2015). In RCTs, research questions aim to investigate the superiority or equivalence of two or more different interventions. When several RCTs investigating a given treatment are available in the literature, systematic reviews and meta-analyses compile the results of these trials. Once enough evidence is available, governmental agencies, focused groups of specialists, or professional's associations write clinical practice guidelines for specific conditions or health problems. In these guidelines, all the available evidence about therapeutic interventions is reviewed to make practical recommendations for clinical implementation based on the quality of evidence. It might be that a treatment has potential benefits, but there are insufficient RCTs, or that there is enough evidence to conclude that a treatment is harmful (Hulley, Cummings, Browner, Grady, & Newman, 2013). Thus, recommendations in clinical practice guidelines take into account two dimensions: the levels of evidence, which are related to the quality of the available studies, and the size of treatment effect, which is the balance between benefits and risks (Table 3, Winstein et al., 2016).

Table 3. Recommendations for clinical practice based on the size of treatment effect (benefit vs risk) and its certainty (levels of evidence).

		Size of treatment effect			
		CLASS I	CLASS IIa	CLASS IIb	CLASS III
		Benefit >>>Risk Treatment should be administered	Benefit >>Risk It is reasonable to administer the treatment*	Benefit ≥ Risk Treatment may be considered±	No benefit/harm
Certainty of treatment effect (Levels of evidence)	LEVEL A Multiple populations evaluated Data derived from multiple randomised clinical trials or meta-analyses	Recommendation that treatment is useful/effective Sufficient evidence from multiple randomised controlled trials or meta-analyses	Recommendation in favour of treatment being useful/effective Some conflicting evidence from multiple randomised controlled trials or meta-analyses	Recommendation that treatment is useful/effective less well established Greater conflicting evidence from multiple randomised controlled trials or meta-analyses	Recommendation that treatment is not useful/effective or may be harmful Sufficient evidence from multiple randomised controlled trials or meta-analyses
	LEVEL B Limited populations evaluated Data derived from a single randomised controlled trial or non-randomised studies	Recommendation that treatment is useful/effective Evidence from single randomised trial or non-randomised studies	Recommendation in favour of treatment being useful/effective Some conflicting evidence from single randomised trials or non-randomised studies	Recommendation that treatment is useful/effective less well established Greater conflicting evidence from single randomised trial or non-randomised studies	Recommendation that treatment is not useful/effective or may be harmful Evidence from single randomised trial or non-randomised studies
	LEVEL C Very limited populations evaluated Only consensus opinion of experts, case studies, or standard of care	Recommendation that treatment is useful/effective Only expert opinion, case studies or standard of care	Recommendation in favour of treatment being useful/effective Only diverging expert opinion, case studies, or standard of care	Recommendation that treatment is useful/effective less well established Only diverging expert opinion, case studies, or standard of care	Recommendation that treatment is not useful/effective or may be harmful Only expert opinion, case studies or standard of care

Adapted from Winstein et al., 2016.

*Additional studies with focused objectives are needed.

±Additional studies with broad objectives are needed.

1.2.6.2 Evidence-based therapies for motor deficits of the upper extremity in stroke rehabilitation

Evidence-based therapies to restore motor function after stroke include repetitive task-specific training, constraint-induced movement therapy, robotic therapy, bilateral training, electrical stimulation, mental practice and virtual reality (Winstein et al., 2016).

As previously described, most of the exercises in stroke motor rehabilitation fall under the approach of task-specific training. Repetitive task-specific training consists of the practice and repetition of functional movements and activities (i.e. skilled-forelimb reaching task, Carr & Sheperd, 1987, 1990). It is based on motor learning principles such as repetition and is task-

oriented. Moreover, it can be combined with other techniques (Winstein et al., 2016). Task-specific training leads to better motor performance together with cortical reorganisation of the affected hemisphere in stroke patients (Hubbard et al., 2015; Pekna et al., 2012).

One of the most studied treatments to enhance motor upper extremity deficits is constraint-induced movement therapy. This therapy restrains the use of the unaffected extremity several hours per day to force the use of the paretic extremity and overcome compensation by learned non-use (Taub & Morris, 2001; Taub, Uswatte, & Pidikiti, 1999). Initially, protocols of this therapy aimed to limit the use of the non-paretic extremity for up to 6-8 hours a day, although a modified version with shorted time periods could be effective as well (Kwakkel, Veerbeek, van Wegen, & Wolf, 2015). Constraint-induced movement therapy has been shown to reduce motor impairment, improve functional movements of the upper extremity and induce cortical reorganisation, especially in stroke patients with active wrist and distal hand movements (Corbetta, Sirtori, Castellini, Moja, & Gatti, 2015).

Robotic therapy refers to devices that provide passive mobilisation, assistance to movements as well as resistance. These devices can be used together with task-specific training or as a form to promote movement repetition. A meta-analysis including 38 trials (n=1206) has shown that robotic therapy in stroke rehabilitation can improve motor control and muscle strength but with little generalisation to other activities (Veerbeek, Langbroek-Amersfoort, van Wegen, Meskers, & Kwakkel, 2017).

Since most of the movements we perform in everyday activities require the integration and coordination of both extremities, bilateral training aims to improve interlimb coupling. However, a systematic review including 11 trials with sufficient quality has concluded that bilateral training is inferior to constraint-induced movement therapy (Lee, Kim, Park, & Park, 2017). Moreover, there is enough moderate-quality evidence showing that unilateral training is superior to bilateral training (Pollock et al., 2014). Thus, it seems that unilateral practice in the form of constraint-induced movement therapy or task-specific training would be more beneficial than bilateral exercises.

Electrical stimulation is used to stimulate paretic muscles with the aim of strengthening voluntary contraction. It can be applied during task performance or to prompt motor behaviour. The stimulation can be manipulated in its frequency, bandwidth, strength and duration. Electrical stimulation seems promising in the acute stage since it can reduce or prevent shoulder subluxation. However, systematic reviews on electrical stimulation point out the high risk of bias in studies investigating this treatment (Eraifej, Clark, France, Desando, & Moore, 2017; Pollock et al., 2014; Vafadar, Côté, & Archambault, 2015).

Mental practice is the training of the mental representation of movements. The patient is asked to imagine task performance. It has been shown that mental practice has a beneficial effect on motor function when combined with conventional treatment (Braun et al., 2013). Motor imagery is feasible and can be used as an adjunct treatment during training sessions but also outside the rehabilitation environment. There is, however, a lack of consensus on its concept, instructions to be given to the patient, timing and dosage (Barclay-Goddard & Thalman, 2011; Harris & Hebert, 2015).

Virtual reality provides a virtual practice environment making use of a virtual display and a motion capture system. The patient is encouraged to play games or perform tasks that involve movements of the upper extremity. Virtual reality can be immersive or non-immersive, it can provide augmented feedback, and it can be remotely monitored, allowing telerehabilitation. A recent meta-analysis concluded that virtual reality is not superior to conventional treatment (Laver et al., 2017). If provided as an add-on treatment, to increase the amount of training compared to a lower dosage of conventional treatment, it can enhance motor function and activities of daily living in stroke patients. One of its advantages is that it allows applying most of the principles of motor learning, increasing the intensity of the training and engaging patients. However, since there are many technologies, virtual environments and tasks that can be used, comparing the results of different studies is puzzling. One of the critical questions is to which extent the same tasks or games that are used in the virtual environment have similar effects in a real environment such as the rehabilitation department. In this line, the EVREST trial has shown that virtual reality is not superior to recreational activities such as playing cards, bingo or board games (Saposnik et al., 2016).

The most recent guideline on stroke rehabilitation (Winstein et al., 2016) offers recommendations of treatments to improve motor deficits after stroke based on the available evidence, its quality and results (Table 4).

Table 4. Recommendations of treatments for upper extremity rehabilitation in stroke.

Class	Level of evidence	Recommendations of treatments for upper extremity rehabilitation in stroke
I	A	Functional tasks should be practiced; that is, task-specific training, in which the tasks are graded to challenge individual capabilities, practised repeatedly and progressed in difficulty on a frequent basis.
I	A	All individuals with stroke should receive ADL training tailored to individual needs and eventual discharge setting.
I	B	All individuals with stroke should receive IADL training tailored to individual needs and eventual discharge setting.
Ila	A	CIMT or its modified version is reasonable to consider for eligible stroke survivors.
Ila	A	Robotic therapy is reasonable to consider to deliver more intensive practice for individuals with moderate to severe upper limb paresis.
Ila	A	NMES is reasonable to consider for individuals with minimal volitional movement within the first few months after stroke or for individuals with shoulder subluxation.
Ila	A	Mental practice is reasonable to consider as an adjunct to upper extremity rehabilitation services.
Ila	B	Strengthening exercises are reasonable to consider as an adjunct to functional task practice.
Ila	B	Virtual reality is reasonable to consider as a method for delivering upper extremity movement practice.
Ilb	B	Somatosensory retraining to improve sensory discrimination may be considered for stroke survivors with somatosensory loss.
Ilb	A	Bilateral training paradigms may be useful for upper limb therapy.
III	A	Acupuncture is not recommended for the improvement of ADLs and upper extremity activity.

These recommendations take into account the size of treatment effect (class) and its certainty (levels of evidence). ADL, Activities of daily living; IADL, Instrumental activities of daily living; CIMT, Constraint-induced movement therapy; NMES, Neuromuscular electrical stimulation. Adapted from Winstein et al., 2016.

1.2.7 Developing new therapies in stroke rehabilitation

Regardless of the existence of clinical guidelines to orient practitioners in applying evidence-based techniques in the field of stroke rehabilitation, there is a complex interaction between clinical practice and research. In other fields of medicine, the implementation of therapeutic interventions is the last stage after decades of investigation with cells lines, animal models and humans. However, in rehabilitation, the clinical application of a therapy usually precedes studies validating its effectiveness. Moreover, there is a lack of standardisation of intervention procedures, and the available evidence is barely incorporated into clinical practice (Bernhardt et al., 2017). Some of the reasons behind a poor translation of research findings into clinical practice are a combination of low methodological quality of studies, lack of agreement in evaluating patients, and poorly defined interventions (Bernhardt et al., 2017). Despite the existence of different therapies to address motor deficits and improve motor function, further

research is needed to improve therapy protocols as well as to elucidate the mechanisms behind the effectiveness of these therapies (Winstein et al., 2016). For example, conflicting evidence exists in the case of mental practice or virtual reality (Barclay-Goddard & Thalman, 2011; Harris & Hebert, 2015; Laver et al., 2017). Redefining an existing treatment or creating a new one is a challenging process because rehabilitation techniques for upper extremity are often complex interventions (Table 5).

Table 5. Dimensions of treatment complexity.

What makes an intervention complex?
Number of interacting components with the experimental and control interventions.
Number and difficulty of behaviours required by those delivering or receiving the intervention.
Number of groups or organisational levels targeted by the intervention.
Number and variability of outcomes.
Degree of flexibility or tailoring of the intervention permitted.

Adapted from Craig et al., 2008.

1.2.7.1 Complexity in rehabilitation techniques.

Rehabilitation techniques to restore motor deficits and improve the functionality of the upper extremity after stroke have several dimensions of complexity.

These types of treatments often comprise numerous components. For instance, a therapy can be designed to be administered in a hospital setting, in group sessions, and using different types of feedback (i.e. visual, somatosensory) and materials. All these components may contribute to the effectiveness of the treatment, and it is difficult to estimate each component's influence on the treatment effect. The fact that rehabilitation therapies have several elements is challenging when selecting a control intervention. In some cases, the experimental and control treatment can have similar components except for a crucial one that is hypothesised to be the one strongly contributing to the treatment success (i.e. type of feedback). In other cases, experimental and control therapies are so different that they may induce different types of behavioural changes (Lohse, Pathania, Wegman, Boyd, & Lang, 2018).

The patient and the therapist's behaviours might often influence the outcome of rehabilitation treatments. As previously described, the patient's motivation or personal factors (i.e. coping style or educational level) are relevant aspects that can modify the involvement of the patient in the treatment and therefore, have an impact on the expected outcome (Plant, Tyson, Kirk, & Parsons, 2016; Sarre et al., 2014). In a similar vein, the expertise of the therapist or their style when conducting the therapy sessions can influence the treatment effect. These behaviours make interventions complex since they are difficult to measure or control.

Rehabilitation therapies can target individual patients but also their caregivers, increasing the number of individuals affected by the intervention.

Although a treatment can be developed to treat motor deficits of the upper extremity, it can also affect other aspects of functioning. For instance, restoring the pattern of movements of the upper extremity can enhance its function as well as the mood and quality of life of the patient. Besides, some motor rehabilitation techniques may also have a cognitive component. Patients may need to sustain attention during practice or make use of working memory due to the requirements of the task. In such cases, although the primary outcome might be clear, a treatment can affect other relevant secondary outcomes that need to be evaluated in research studies.

Finally, behavioural treatments are often adapted to the needs of the patient (i.e. the degree of impairment), which leads to tailored treatments for each patient. This fact is particularly complex to address in experimental designs where the overall performance of a group is tested.

1.2.7.2 Developing and evaluating complex interventions

The Medical Research Council provides a framework and a guide for the process of developing, evaluating and implementing complex interventions (Craig et al., 2008). The process includes the stages of developing, piloting, evaluating, reporting, and implementing a complex intervention (Figure 15).

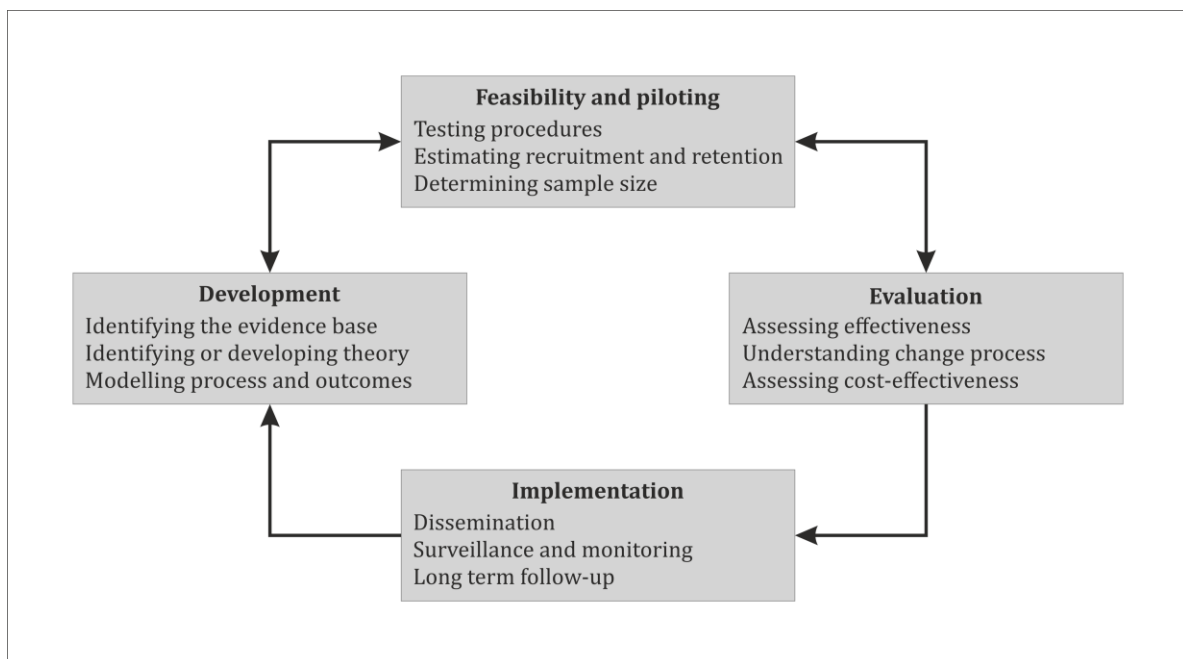


Figure 15. Process for developing, evaluating and implementing complex interventions.
Adapted from Craig et al., 2008.

Developing an intervention. In the development of a new intervention, the first step is the definition of the treatment, its procedures and its outcome.

In this early stage, the review of previous evidence is necessary to have a clear theoretical understanding of how the treatment is likely to affect the outcome. Modelling can be used to refine the therapy protocol as well as to select the most relevant outcome (Eldridge et al., 2005). When defining the treatment, a particular focus should be placed on the feasibility of the therapy to be implemented in a clinical setting. In addition to evidence review, information gathered from patients, therapists and stakeholders might be useful to adapt the intervention protocol (Craig et al., 2008). The selection of outcomes in stroke rehabilitation should take into account which level of functionality within the ICF a specific treatment is targeting. Improvements in functioning can be measured at the level of brain networks, body structure and function, autonomy in activities of daily living, and participation and roles of the individual (Table 6).

At the neural level, measures of brain structure and function include Magnetic Resonance Imaging, Magnetoencephalography, Electroencephalography and Event-related potentials, or Transcranial Magnetic Stimulation, among others. These techniques allow the study of brain structure and its activity at rest or during task performance. Measurements at this level can be used to characterise the sample, as biomarkers to make predictions of recovery or as a measure of plastic changes over time if used longitudinally. Importantly, different measures of brain plasticity can vary in significance depending on the time point of the evaluation or treatment tested (Dobkin, 2004).

Table 6. Measurements used in stroke motor rehabilitation.

Measurements used in stroke motor rehabilitation			
Health condition and Body structure and function (neural level)	Body structure and function (movement level)	Activity	Participation
Magnetic Resonance Imaging	Kinematic movement analysis	Action Research Arm Test	Stroke-specific Quality of Life Scale
Magnetoencephalography	Electromyography	Box and Blocks Test	Stroke Impact Scale
Event-related potentials	Muscle strength	Nine Hole Pegboard Test	General health questionnaire
Transcranial Magnetic Stimulation	Fugl-Meyer Assessment of Motor Recovery after Stroke	Wolf Motor Function Test	Health survey questionnaire SF-36
	Motricity Index of Motor Impairment after Stroke		

Examples of measurements used in stroke motor rehabilitation to evaluate the health condition, body structure and function at the neural and movement level, activity and participation.

Behavioural assessments can measure the motor impairment and the functional use of the upper extremity in tasks or activities. The evaluation of the motor impairment falls under the category of the body structure and function of the ICF and it is of particular interest to know if true recovery has occurred (Kwakkel et al., 2004). The evaluation of the motor impairment is focused on how movements are performed and can include kinematic movement analysis, electromyography, muscle strength, the Fulg-Meyer motor assessment or the Motricity Index of Arm. At the activity level, the focus of the evaluation is on the ability of the patient in performing tasks or activities. The Action Research Arm Test, the Box and Blocks Test, the Nine Hole Pegboard Test, or the Wolf motor function test are examples of measurements of upper extremity motor ability. Some of these measures do not take into account the movement quality and only evaluate task achievement. Motor impairment and limitations in activities are often evaluated in clinical trials. However, how a motor intervention affects the participation of the patient in their community life is often unexplored in studies (Salter, Foley, Jutai, & Teasell, 2007). Participation can be measured with self-administered questionnaires of quality of life such as the Stroke-specific Quality of Life Scale that include items about roles, relationships and community activities.

This conceptual stage, where treatment, procedures and outcomes are defined, is not only needed when developing a new therapy but also before modifying an existing one.

Piloting and feasibility. Adequate piloting is a crucial preparatory work that will inform about the rate of recruitment and withdrawal, the acceptability of the treatment by patients, treatment compliance and delivery as well as treatment effect (Craig et al., 2008). The importance of piloting is often underestimated, it can however prevent future problems in the recruitment, compliance and expected effect sizes (Feeley et al., 2009).

Regarding effect sizes, for most of the behavioural measures, the Minimal Detectable Change (MDC) and the Minimal Clinically Important Difference (MCID) have been established and are relevant psychometric properties for clinical research. Both the MCD and MCID estimate the amount of change that represents a noticeable improvement in ability or a change that is perceived as clinically important by the patient or clinician (Lin et al., 2010; Wright, Hannon, Hegedus, & Kavchak, 2012). The incorporation of these psychometric properties in data analyses might be useful to detect clinically relevant changes that are not statically significant or, in a reverse way, to consider with caution statistically significant changes that are not clinically meaningful. When piloting, effect sizes can be bigger or smaller when compared to studies with larger samples. Thus, a series of pilot studies may be necessary before embracing large trials.

Evaluating the intervention. Several research designs are available and suit different questions and circumstances. This stage aims to assess the effectiveness of a treatment, understand underlying processes, and estimate cost-effectiveness (Oakley, Strange, Bonell, Allen, & Stephenson, 2006). Ideally, RCTs are the gold standard research designs to test for effectiveness (Figure 16).

Usually, studies of motor stroke rehabilitation compare two or more techniques to determine whether or not one treatment is more effective than the other or provides equal benefits. In the acute and subacute phases of stroke rehabilitation, it would be unethical to leave patients without a treatment that has been proven to be beneficial and very often the control and experimental groups receive usual care or conventional treatment. This fact is particularly tricky because, in most clinics, usual care is a combination of more than one technique or approach (Lohse et al., 2018). Thus, it is difficult to compare two treatments alone in the acute and subacute stages and most often a combination of treatments is investigated. In the case of the chronic stage, stroke patients usually do not receive any kind of rehabilitation. Thus, studies conducted in this stage compare the experimental group to a control group of patients who do not receive treatment. However, under the premise that any behavioural intervention can lead to a change, special attention needs to be given when concluding that the changes observed in the experimental group are due to the specific components of the therapy. The improvement of the experimental group when compared with a group that has not received any treatment can be explained by the effect of just providing an activity. These challenges in the design and definition of treatments often result in a lack of a proper control group.

Moreover, rehabilitation studies usually have convenient samples with a small number of participants. Samples are often heterogeneous in the type and location of the stroke, time since the injury and severity of deficits. The number of participants and their heterogeneity makes it extremely difficult to generalise the results, affecting the external validity of studies. Further research from multicentre studies and the stratification of patients by severity or neural biomarkers is needed to move forward. Importantly, an economic evaluation of the cost of the treatment can provide insights regarding the balance between effectiveness and economic investment, which is a crucial issue for health policy decision-makers.

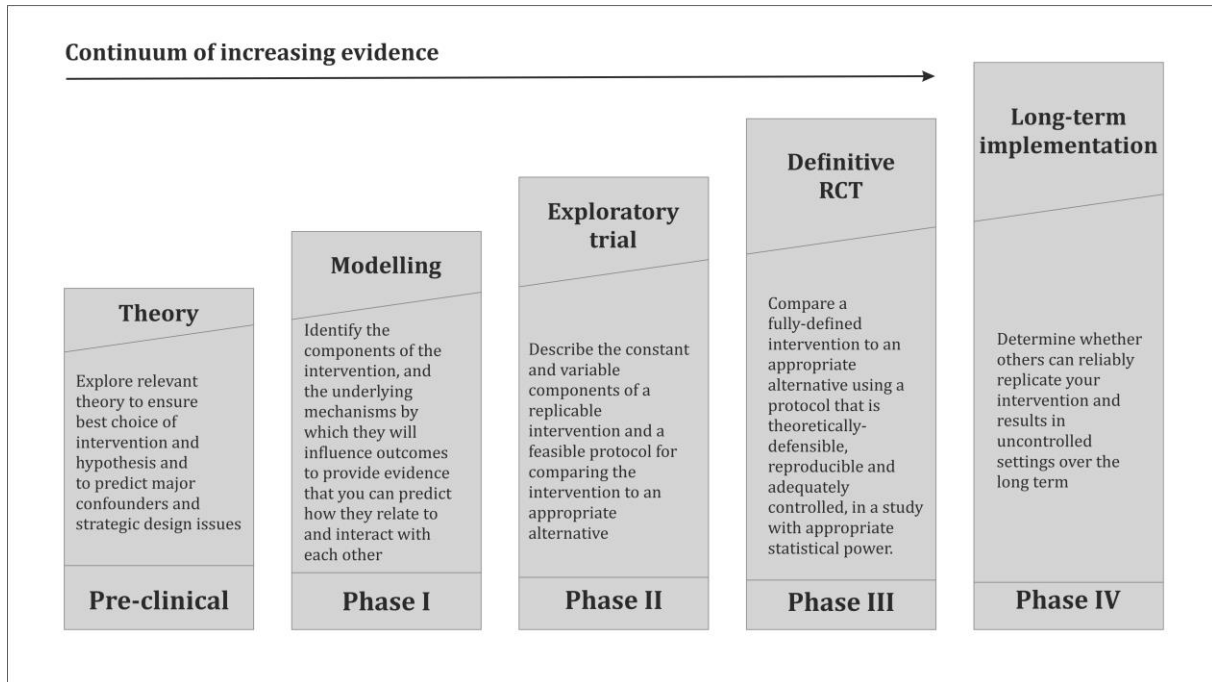


Figure 16. Continuum of increasing evidence.

Adapted from Lovell et al., 2008.

Reporting. Reporting is a central element in this process. It should be viewed as a transversal activity to be done in each one of the stages. Scientific reporting aims to communicate results, enable replication and update systematic reviews on the topic (Möhler, Köpke, & Meyer, 2015). In studies of stroke rehabilitation, descriptions of treatments are often incomplete in the literature. A recent systematic review examined a total of 215 studies of motor rehabilitation in stroke and found that treatments were poorly defined (Lohse et al., 2018). Specifically, research articles fail at reporting how the experimental therapy is tailored to the individual as well as which was the treatment compliance. This scenario is even worse for control treatments. Materials and procedures of control therapies are poorly described and referenced even when they are referred as conventional or usual care. This fact represents a methodological problem when combining results from different studies to conduct meta-analysis. The template for intervention description and replication (TIDieR) provides a checklist of relevant aspects that should be described to allow replication (Hoffmann et al., 2014). The name of the treatment should be provided and kept consistent among studies. In addition, a description of the rationale or theory behind the intervention is necessary. Regarding the treatment sessions, there is a need of providing information about the procedures and activities as well as the materials used in the delivery of treatment, the setting where the therapy is administered, and the professional who provides the treatment (Glasziou, Meats, Heneghan, & Shepperd, 2008). About the dosage, it is particularly important to describe the number of sessions and their duration and how these were scheduled (Bernhardt, Borschmann, et al., 2017). Additionally, standardised

measurements are needed to monitor treatment administration and account for variations in the protocol.

Implementation. Implementation not only depends on publishing the results in scientific articles but also on convincing decision-makers and identifying the facilitators and barriers to implementing the treatment. Some strategies might involve stakeholders in the research process to agree on relevance or summarising evidence comprehensively. To implement a treatment in a given environment (i.e. inpatient rehabilitation department), a comprehensive analysis of the required changes regarding human resources, physical space, materials or department organisation is critical to developing strategies to change current behaviours (Craig et al., 2014). Furthermore, implemented treatments need to be monitored to identify possible adverse effects or retention of gains in the long-term that are difficult to study using experimental designs.

1.2.8 Interim summary: stroke rehabilitation

Motor deficits after a stroke impair the ability to perform movements, and lead to limitations in activities and restrictions on participation, affecting the individual's functioning at many different levels. The rehabilitation process aims to improve and maintain functioning through restitution, substitution and compensation of functions using therapeutic interventions to promote adaptive learning (Langhorne et al., 2011; Selzer et al., 2006). However, recovery will depend on the ability of the brain to adapt to the injury and the capacity of therapeutic interventions to induce brain reorganisation and promote functional recovery (Krakauer et al., 2012).

After the stroke, changes in blood flow, inflammation, edema and diaschisis hinder the ability of the brain to maintain functioning. With time, these processes are naturally reduced, which explains the outstanding spontaneous biological recovery observed in the initial days and weeks after stroke (Kwakkel et al., 2004). Importantly, after the brain injury, the expression of growth-promoting genes induces dendritic remodelling, axonal sprouting and synaptogenesis (Krakauer et al., 2012). This is of particular clinical relevance because therapeutic interventions can take advantage of this favourable cellular environment for the establishment of new connections to promote learning-dependent plasticity through experience (Buma et al., 2013; Dancause & Nudo, 2011).

Since the early nineties, it has been evidenced that brain reorganisation, and especially changes in cortical motor map representation, can occur after stroke with training (Nudo et al., 1996). Of much debate has been whether inter- or intra-hemispheric reorganisation is associated with better outcomes. The bimodal balance-recovery model proposes that reorganisation within the

lesioned or the unaffected hemisphere will depend on the amount of structural reserve to sustain function (Di Pino et al., 2014). The mechanisms at a system level that underpin hemispheric reorganisation are compensation, degeneracy and neural and cognitive reserve, which are adaptive mechanisms; and diaschisis, transneuronal degeneration and dedifferentiation, which are maladaptive mechanisms (Fornito et al., 2015).

One of the clinical implications of understanding the biological mechanisms of neuroplasticity and their time course is to plan therapeutic interventions adequately. The last consensus framework classifies stroke recovery stages into hyper-acute, acute, early and late subacute and chronic (Bernhardt, Hayward, et al., 2017).

Stroke rehabilitation aims to induce and modulate plasticity through experience using two main approaches: training and enriched environment (Buma et al., 2013). On the one hand, training refers to therapeutic interventions where the patient actively engages in a process of motor skill learning. Several principles derived from basic research on motor learning have been shown to boost skill acquisition (Wulf & Lewthwaite, 2016). To name a few, training should be task-specific, relevant for the individual, and involve mass practice of movements. Besides, how instructions and guidance are provided or the type of feedback and reinforces influence learning. On the other hand, enriched environment is an approach mainly investigated in animal models whose cage conditions have been modified to sensory stimulate the animals and promote their activity (Johansson, 1996). Although these conditions are more difficult to test in humans using experimental designs, the strong evidence behind enriched environment in animal models suggests that an environment that is rich and varied in stimuli and promotes exercise and participation in different activities enhances the potential for recovery (Janssen et al., 2014; Komitova et al., 2005).

In clinical practice, the available evidence and its quality are crucial elements for the acceptance and implementation of rehabilitation techniques since therapeutic interventions provided to patients should be evidence-based. The most recent guideline of stroke rehabilitation recognises that repetitive task-specific training, constraint-induced movement therapy, robotic therapy, bilateral training, electrical stimulation, mental practice and virtual reality are effective techniques to rehabilitate motor deficits after stroke (Winstein et al., 2016). However, conflicting evidence exists in some therapies and in other cases, more research is needed to clearer define protocols or to replicate their positive effects. The field of stroke rehabilitation faces several challenges in designing and evaluating rehabilitation techniques, mainly because these interventions are complex. To develop a complex intervention, the Medical Research

Council proposes guidelines for developing and evaluating interventions with stages that consist of developing, piloting, evaluating, reporting, and implementing (Craig et al., 2008).

Despite the existence of motor rehabilitation techniques, further work needs to be done to design and test interventions with a strong grounding in basic research. Ideally, new therapies should involve motor skill learning, be task-specific and relevant for the individual. Elements derived from research on motor learning such as mass repetition of movements, feedback, reinforces, instructions and modelling should be incorporated. Moreover, new therapeutic interventions should promote mechanisms of adaptive plasticity through training. From the two main behavioural approaches in rehabilitation, training and enriched environment, elements of the first seem feasible to incorporate in new training paradigms. However, new therapies should also include components of the latter approach. Sensory feedback, varied stimuli and joyfulness in the task could actively engage and stimulate the patient. In this vein, music-based interventions for stroke motor rehabilitation have emerged as a promising tool capable of integrating most of the relevant principles of training and multimodal stimulation.

1.3 Music in stroke rehabilitation

Musical activities such as listening, playing, signing or dancing are common activities in our daily lives. The therapeutic use of these leisure activities relies on the ability of music in inducing emotions and regulating mood. Moreover, these activities require highly skilled movements and the perception and integration of information from different modalities, placing high demands on the nervous system. Music has been used to treat several conditions throughout human history. In the case of stroke rehabilitation, music-based interventions can be used as a training to overcome different motor and cognitive deficits and as a form of multimodal stimulation to enhance cognition, engage patients, and increase their motivation and well-being.

The following sections review music-based interventions to treat upper extremity motor deficits in stroke rehabilitation.

1.3.1 Making music after stroke

The main music-based approach to treat the hemiparesis of the upper extremity after stroke is playing musical instruments. This activity aims to enhance the motor function by providing a context for motor skill learning. It is regarded as an active intervention because the patient actively engages in training that requires the execution of movements to create music.

Playing an instrument requires highly coordinated fine movements that need to be precise in their timing and spatial organisation. In the planning and execution of complex sequences of movements, the basal ganglia, supplementary motor area, premotor, motor and somatosensory cortices, and cerebellum are all involved. All these regions play different roles in sequencing movements in the correct timing, predicting and controlling movement trajectories, and monitoring errors for online motor adjustments (Cunningham, Machado, Yue, Carey, & Plow, 2013; Guo, Ke, & Raymond, 2014; Herrojo Ruiz, Brücke, Nikulin, Schneider, & Kühn, 2014; Jin & Costa, 2015; Nambu et al., 2015; Sun et al., 2015). In music playing, movements are performed to produce an outcome: the sound of the instrument. A precise mapping between the sound and the movement to produce it is needed when playing music (Chen, Rae, & Watkins, 2012). The areas responsible for controlling and adjusting how movements need to be organised in space are the parietal, sensorimotor and premotor cortices (Zatorre, Chen, & Penhune, 2007). When listening to the instrument sound, projections from the primary auditory cortex to parietal regions are important to create auditory-motor transformations and enhance the association between sound and movement (Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Hickok & Poeppel, 2004; Patel, 2006). In this sense, there is a complex audio-motor interplay that involves feedforward and feedback loops (Zatorre et al., 2009).

When planning a movement, internal motor representations are used to make predictions of what the outcome will be. The motor plan is modulated by these predictions and thus, anticipating the desired sound (movement outcome) influences the motor output in a feedforward loop. When the movement is performed, the sound is evaluated and compared to the auditory expectations that were created by internal representations. Thus, the auditory feedback is used to evaluate the motor performance and make on-line motor adjustments (D'Ausilio, Brunetti, Delogu, Santonico, & Belardinelli, 2010; Furuya & Soechting, 2010). This sensory-motor interplay requires the coactivation of auditory and motor regions. It has been shown that motor and premotor cortices are activated when musicians listen to well-trained melodies (Haueisen & Knösche, 2001). On the other hand, when musicians play silent instruments, auditory regions can be activated. These examples support the idea of audio-motor coupling in music making. Audio-motor coupling reflects the coupling between perception and action and has been observed not only in musicians but also in healthy individuals after short training sessions with a musical instrument (Bangert et al., 2006).

Music training leads to functional and structural changes not only in a wide variety of motor brain regions but also in other areas relevant to the task (Altenmüller & Schlaug, 2015; Dayan & Cohen, 2011; Draganski et al., 2004; Draganski & May, 2008; Schlaug, 2015). For example, when non-musicians learn to play piano sequences, the cortical representation of flexor and extensor

finger muscles can experience an enlargement that is associated with improved performance in the piano task (Pascual-Leone et al., 1995). Thus, this type of training could be beneficial to promote plastic changes and the recovery of motor brain regions in stroke patients.

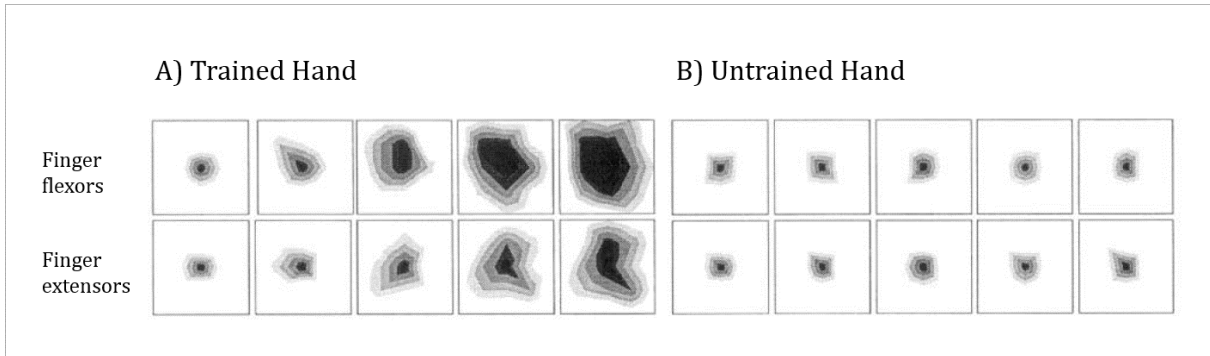


Figure 17. Cortical representation of hand muscles during musical training.

The cortical representation of finger flexors and extensors is shown for the trained and untrained hand. Each column represent a day in a 5-day training protocol. In the trained hand, there is an enlargement of the cortical map. Adapted from Pascual-Leone et al., 1995.

Music playing is not only highly demanding on the motor system. Cognitive processing is also required in musical activities. For instance, attention and working memory are needed to keep track of the timing and remember melodies and lyrics (Särkämö et al., 2013). Moreover, music is a powerful stimulus to influence and modulate emotional states. Since melodies can express different emotions, emotional networks are activated to perceive and recognise the emotional aspects of music. These networks include the frontal lobe, cingulate gyrus, amygdala, hippocampus and midbrain (Salimpoor, Benovoy, Longo, Cooperstock, & Zatorre, 2009; Salimpoor, Zald, Zatorre, Dagher, & McIntosh, 2015).

Music-based interventions can incorporate many principles of stroke motor rehabilitation. What makes these interventions different from other motor rehabilitation techniques is the multisensory nature of musical activities, which may be beneficial for learning and could be a critical aspect in explaining the effectiveness of music-based therapies (Zimmerman & Lahav, 2012). As mentioned before, some of the well-accepted principles in stroke motor rehabilitation are that training should be task-specific and goal-directed, and involve mass repetition of movements. Training in playing an instrument after stroke aims to learn a specific skill that requires highly coordinated fine movements. The use of musical instruments allows increasing the complexity of musical sequences and melodies as patients progress and their mobility improves, adapting the exercises to the individual needs of each patient. Playing an instrument demands not only the execution of complex movements but also the perception and processing of sounds. This action-perception cycle is an excellent scenario to work with patients with motor deficits since the auditory output can serve as valuable feedback for motor performance.

Providing a context of motor skill acquisition, musical training in stroke aims to induce similar neural plastic changes than those occurring in healthy individuals when they learn to play an instrument. Importantly, music-based interventions are regarded as meaningful activities, perceived as playful and enjoyable by patients. This may boost the patients' engagement and motivation and increase motor learning and performance (Särkämö et al., 2013).

1.3.2 Music-based interventions to treat motor deficits after stroke

Several studies have investigated active music-based interventions for the rehabilitation of upper extremity motor function in stroke (Table 7). These include Music-supported Therapy (Schneider, Schönle, Altenmüller, & Münte, 2007), Music glove (Friedman et al., 2014), Therapeutic instrumental music performance (Street et al., 2018), Music upper limb therapy-integrated (Raghavan et al., 2016), Active music therapy (Raglio et al., 2017), Rhythm- and music-based therapy (Bunketorp-Käll, Lundgren-Nilsson, Samuelsson, et al., 2017) and Musical sonification therapy (Scholz et al., 2016).

The studies summarised in Table 7 make use of different research designs such as RCTs, experimental designs, case-series and case-studies. Overall, there are eight RCTs and three experimental studies that although having a control group, randomisation of patients into groups was not done. Moreover, three experimental studies have investigated music therapy without comparing its effects to other treatment, and a case-series and a case-study. Of these studies, six of them have tested the effectiveness of music-based interventions in the early subacute phase of stroke recovery. Ten of them have been performed in the late subacute or chronic phase. In the early subacute phase, music-based interventions were added to the standard program of rehabilitation. Music therapy as an add-on treatment was compared to other types of interventions (sham therapy or modifications of the music therapy protocol) or standard care. In the chronic phase, music-based interventions were compared with no treatment, other types of treatment such as horse riding, self-guided hand exercises, or mute versions of the musical training.

Regarding the primary outcome, most of these studies have investigated the effectiveness of music-based interventions primarily in improving the motor function of the upper extremity. Other studies, however, investigated the effectiveness of these therapies in improving the perception of recovery, physical and cognitive disability, and motor impairment.

Reference	Study design	Music-based intervention	Control treatment	Participants (n) Recovery phase	Primary outcome	Duration of intervention	Main results
Street et al., 2018	RTC Cross-over design	Therapeutic instrumental music performance	No	10 Late subacute and chronic phase	Feasibility of treatment	6 weeks 12 sessions 6 hours	Participants perceived the musical intervention as motivating, and that instruments facilitated movements. Patients reported that fatigue was low. Music therapy seems feasible.
Bunketorp-Käll et al., 2017a Bunketorp-Käll et al., 2017b	RCT 3-armed	Rhythm- and music-based therapy	Horse-riding therapy No treatment	122 Chronic phase	Perception of stroke recovery SIS, item 9	12 weeks 24 sessions Rhythm- and music-based therapy: 36 hours Horse-riding therapy: 96 hours	Perception of recovery was greater for patients treated with rhythm- and music-based therapy and horse-riding therapy and was maintained at 3 and 6-month follow up. Horse-riding therapy group improved in gait and balance, and rhythm- and music-based therapy group in balance and grip strength. Improvements were maintained at 6 months. Patients treated with rhythm- and music-based therapy showed increased working memory at 6 months. Caregiver burden was reduced in the rhythm- and music-based and horse-riding therapy groups after the therapy and at 3-month follow-up.
Zondervan et al., 2016	RCT 2-armed Cross-over design	Home music glove	Self-guided hand exercises	17 Chronic phase	Motor function BBT	3 weeks 9 hours	Both groups improved in the functional use of the upper extremity.
VanVugt et al., 2016	RCT 2-armed	Music-supported Therapy	Music-supported Therapy with delayed feedback	34 Early subacute phase	Motor function 9HPT	4 weeks 10 sessions 5 hours	Both groups improved upper extremity function, but improvements were more prominent in the delayed feedback group.
Tong et al., 2015	RCT 2-armed	Music-supported Therapy	Mute Music-supported Therapy	30 Late subacute and chronic phase	Motor function WMT	4 weeks 20 sessions 10 hours	Both groups improved but greater improvements were seen in the experimental group.
Friedman et al., 2014	RCT 2-armed	Music glove	Self-guided hand exercises	12 Chronic phase	Motor function BBT	2 weeks 6 sessions 6 hours	Both groups improved but a major improvement was observed in the Music glove group.
Altenmüller et al., 2009	RCT 2-armed	Music-supported Therapy	Standard care	62 Early subacute phase	Motor function ARAT	3 weeks 15 sessions 7.5 hours	The experimental group improved in the functional use of the affected extremity and movement kinematics. An enhancement of connectivity between motor and auditory regions was found in the music group.
Schneider et al., 2007	RCT 2-armed	Music-supported Therapy	Standard care	20 Early subacute phase	Motor function ARAT	3 weeks 15 sessions 7.5 hours	Major improvements in the functional use of the affected extremity and movement kinematics in the experimental group.
Raglio et al., 2017	Experimental study	Active music therapy approach	Standard care	38 Early subacute phase	Physical and cognitive disability FIM	7 weeks 20 sessions 10 hours	Increased grip strength in the experimental group. Both groups improved their quality of life, functional level and gross mobility.

Continuation							
Reference	Study design	Music-based intervention	Control treatment	Participants	Primary outcome	Duration of intervention	Main results
Scholz et al., 2016	Experimental study	Musical sonification therapy	Sham sonification	25 Early subacute phase	Motor impairment FMA	10 sessions 5 hours Unknown weeks	Both groups improved the functional use of the affected extremity but the group treated with musical sonification therapy experienced a reduction in pain after training.
Ripollés et al., 2016 Amengual et al., 2013	Experimental study	Music-supported Therapy	No	20 Chronic phase	Motor function ARAT	4 weeks 20 sessions 10 hours	Improvement in the functional use of the affected extremity and movement kinematics, attention, speed of processing, and rate of verbal learning after the therapy. Patients increased their arousal, valence, positive affect and quality of life, and reported less depressive symptoms. A pattern of intrahemispheric reorganization within the lesioned cortex was observed after the therapy, with cortical map reorganization and increased excitability of the motor cortex, and functional coupling between motor and auditory areas.
Raghavan et al., 2016	Experimental study	Music upper limb therapy-Integrated	No	13 Chronic phase	Motor impairment FMA	6 weeks 12 sessions 9 hours	Reduced upper limb motor and sensory impairment, and activity limitation. Patients increased their well-being and participation.
Van Vugt et al., 2014	Experimental study	Music-supported Therapy in pairs	Music-supported Therapy in turns	28 Early subacute phase	Motor function 9HPT	3-4 weeks 10 sessions 5 hours	Patients treated in turns improved more in the functional use of the affected extremity. Both groups improved in movement kinematics. Both groups reported less fatigue and depressive symptoms.
Villeneuve et al., 2014	Experimental study	Home Music-supported Therapy	No	13 Chronic phase	Motor function BBT/9HPT	3 weeks 9 sessions 9 hours	Overall motor function improvement after the therapy.
Villeneuve et al., 2013	Case series	Home Music-supported Therapy	No	3 Chronic phase	Motor function BBT/9HPT	3 weeks 9 sessions 9 hours	Improvement in note and timing accuracy within and across the training sessions together with motor function improvement after the therapy.
Rojo et al., 2011	Case-study	Music-supported Therapy	No	1 Chronic phase	Motor function ARAT	4 weeks 20 sessions 10 hours	Improvement in the functional use of the affected extremity and movement kinematics. Reorganisation within the lesioned hemisphere, with increased excitability, cortical map reorganisation and functional coupling between motor and auditory areas.

Table 7. Summary of studies investigating music-based interventions for the upper extremity motor rehabilitation in stroke.

ARAT, Action Research Arm Test; BBT, Box and Blocks Test; CIMT= Constraint-induced movement therapy; FIM, Functional Independence Measure; FMA, Fugl-Meyer Assessment of Motor Recovery after Stroke; RCT, Randomised Controlled Trial; SIS, Stroke Impact Scale; WMT, Wolf Motor Function Test; 9HPT, Nine Hole Pegboard Test.

1.3.2.1 Music-supported Therapy

One of the most investigated protocols of music-based interventions to treat hemiparesis after stroke is Music-supported Therapy (Schneider et al., 2007). In this therapy, stroke patients are trained to play musical instruments with the affected upper extremity to enhance motor performance. In the training sessions, an electronic keyboard and drum pads are used in an adapted form to exercise fine and gross movements respectively. A standardised protocol of different exercises arranged into levels of increasing difficulty has been designed and allows the individualisation of the training regarding the severity of motor deficits (for a detailed description of the treatment, see Appendix). Patients may start playing simple sequences, which progressively increase in complexity, and eventually evolve into playing folk songs at the end of the training period. Music-supported Therapy aims to promote motor skill learning and is based on the principles of (i) mass repetition of finger and arm movements; (ii) audio-motor coupling and integration; (iii) shaping; and (iv) emotion-motivation effects (Rodriguez-Fornells et al., 2012).

Mass repetition of finger and arm movements: As previously described, mass repetition of movements is a well-known principle of motor learning and rehabilitation. If repetition of movements is embedded in a context of learning, where feedback, and movement and context variations are provided, motor performance will be facilitated (Kitago & Krakauer, 2013). In Music-supported Therapy, the patient is trained to intensively practice movement sequences with the affected extremity to overcome the motor deficits and improve their motor ability. Importantly, Music-supported Therapy allows to shape the difficulty of movement sequences gradually, and thus, tailor the training to the individual needs of the patient. The use of an electronic keyboard and drum pads involve movements of finger and hand tapping. Thus, this training requires movements of flexion and extension of the fingers, wrist, and elbow, as well as shoulder adduction and abduction, elevation and internal and external rotation. By repeating these types of movements, the training is aimed at enhancing the range of movement, speed and coordination of the upper extremity.

Audio-motor coupling: When the patient is performing a movement with the affected extremity (pressing a key or hitting an electronic pad), a sound is produced by the musical instrument. This auditory feedback, which is the outcome of the movement, serves two purposes for the nervous system. Firstly, the auditory information is used to evaluate the motor performance, allowing the patient to note well-performed movement sequences and also to notice and correct errors when needed. Importantly, feedback that is coupled to the movement might be more effective in improving motor performance (Schmidt, 2005). Secondly, when the

movement is associated with a sound, internal motor representations can predict what the auditory outcome will be and thus, the motor plan can be adjusted according to this outcome prediction. These two aspects might be especially crucial since it has been shown that stroke patients can experience deficits in processing proprioceptive information (Mercier, Bertrand, & Bourbonnais, 2004), and therefore in updating the internal representation during movement performance (Barany, Della-Maggiore, Viswanathan, Cieslak, & Grafton, 2014; Ghez, Gordon, & Ghilardi, 1995). The presence of sounds coupled with movements of the paretic extremity in Music-supported Therapy might be a critical aspect since it could counteract proprioceptive deficits.

Shaping: One relevant factor to facilitate motor learning is the gradual approximation to desired performance. The standardised protocol of Music-supported Therapy facilitates playing regardless of the patient' motor ability. By dividing the task into multiple levels and adapting the difficulty of movements to the needs of the patients, the protocol aims at reducing the perceived task difficulty and promoting positive emotions and feelings of self-efficacy.

Emotion-motivation effects: Music is a powerful regulator of mood, being capable of inducing different emotions in the listener and activating brain regions associated to reward (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011; Zatorre & Salimpoor, 2013). Moreover, playing musical instruments is an activity that has real-world relevance, and is often perceived as enjoyable by patients. Motivation towards the task is an essential factor in motor learning. In stroke patients, successfully instrument playing could increase feelings of self-efficacy and agency, as patients perceive they are learning a new skill.

Music-supported Therapy has been shown to enhance the motor function and movement kinematics of the paretic extremity in stroke patients (Amengual et al., 2013; Schneider et al., 2007). Two RCTs in the early subacute phase of stroke recovery have shown that adding Music-supported Therapy to the rehabilitation program was superior in improving the motor function of subacute stroke patients than standard care alone (Altenmüller, Marco-Pallares, Münte, & Schneider, 2009; Schneider et al., 2007). Interestingly, chronic stroke patients can also enhance their upper extremity functionality when treated with Music-supported Therapy, even when the treatment is provided years after the stroke (Amengual et al., 2013; Rojo et al., 2011). It could be argued that the observed behavioural motor improvement is due to undergoing high-intensity training with mass repetition of movements. Following this reasoning, any therapy with exercises involving finger and arm movements could lead to the same results. However, the study of Ripollés and colleagues (2016) might offer an interesting perspective on the role of the auditory feedback in Music-supported Therapy (Ripollés et al., 2016). In this study, a group of

chronic stroke patients was evaluated with functional Magnetic Resonance Imaging when performing an auditory task. Patients listened to the trained melodies, before and after a four-week program of Music-supported Therapy. At baseline, the passive listening of melodies (at this time-point, untrained melodies) elicited activations in auditory regions of both hemispheres and motor areas of the unaffected hemisphere. However, motor regions of the affected hemisphere were not activated, which could indicate a disruption in the audio-motor network of stroke patients. Interestingly, after the training, motor regions of both hemispheres, such as the precentral gyrus and supplementary motor area, were activated when the melodies were heard (Figure 18A). An analysis of functional connectivity showed an increase in the co-activation between the supplementary motor area, the precentral gyrus, and the inferior frontal gyrus with the primary auditory cortex. Moreover, there was an enhancement of connectivity between the mentioned motor regions of the affected hemisphere (Figure 18B). These results would suggest that the presence of the auditory feedback during the training could lead to the re-establishment of audio-motor coupling.

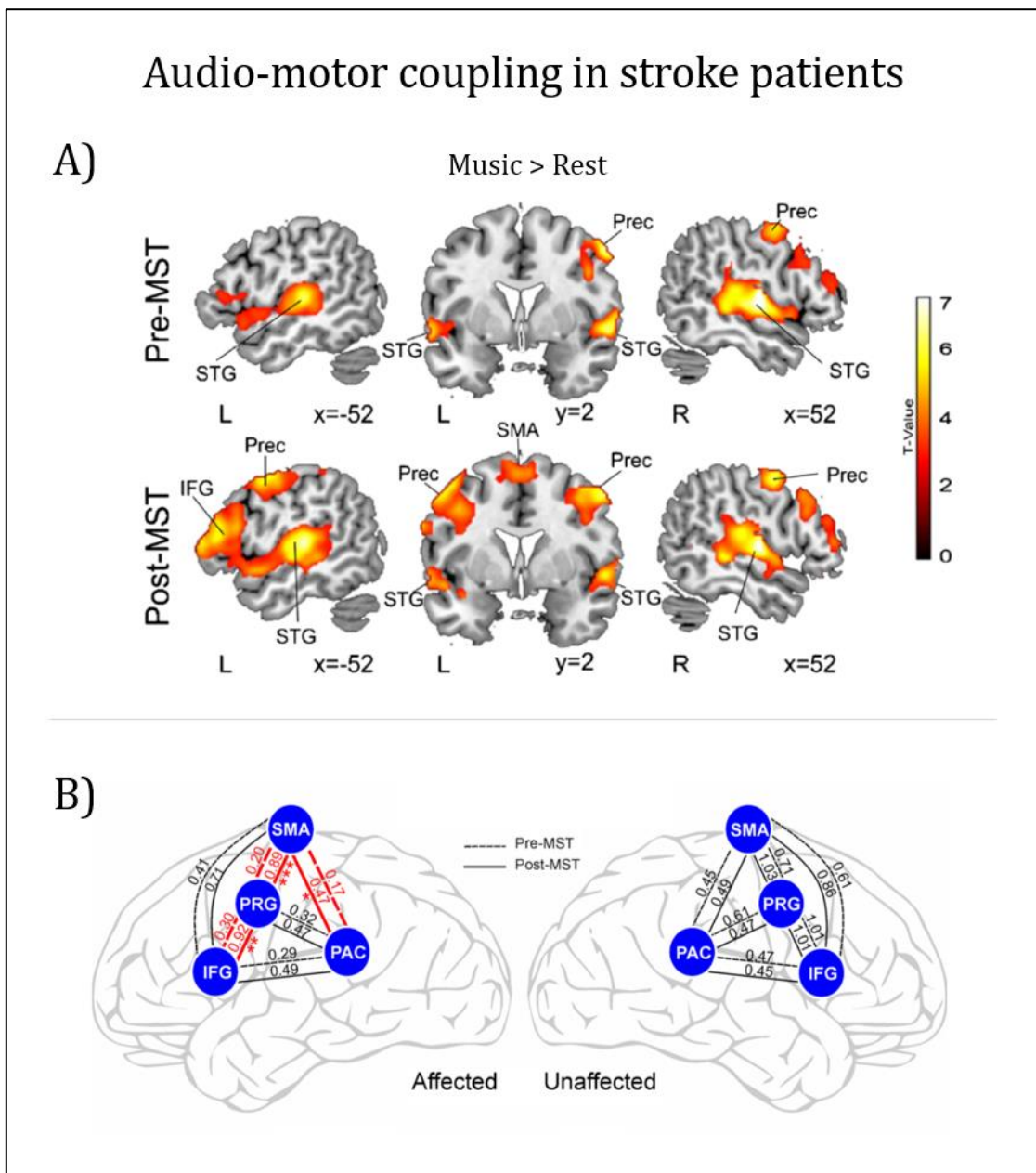


Figure 18. Audio-motor network in chronic stroke patients treated with Music-supported Therapy. A) Before the training (Pre-MST), the passive listening of melodies lead to activations in the superior temporal gyrus of both hemispheres, and the precentral gyrus of the unaffected hemisphere (right hemisphere). After the training (Post-MST), motor regions of the affected hemisphere (left hemisphere) were also activated, along with the regions that were active in the pre-treatment evaluation. B) Functional connectivity analysis between motor regions (supplementary motor area, precentral gyrus and inferior frontal gyrus) and the primary auditory cortex before and after Music-supported Therapy. Adapted from Ripollés et al., 2015.

In this same study, patients also did a motor task inside the scanner, consisting of simple finger tapping movements. Before the treatment, patients exhibited bilateral motor activations when moving the affected hand. This indicates a pattern of functional reorganisation based on compensation and dedifferentiation since the ipsilateral motor network is activated to support functioning. After the training, the involvement of the unaffected hemisphere was reduced when

moving the affected hand, which suggests that the training promotes functional reorganisation within the affected hemisphere (Figure 19).

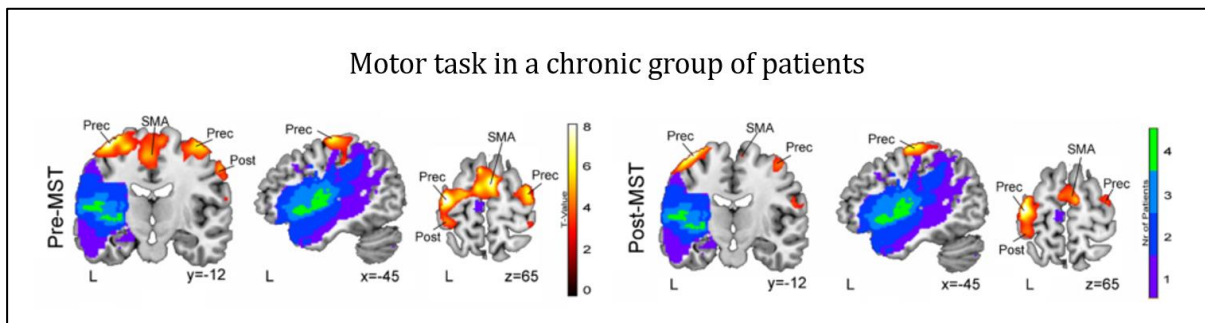


Figure 19. Motor reorganisation in chronic stroke patients treated with Music-supported Therapy. activations associated with movements of the paretic hand in a group of stroke patients treated with Music-supported Therapy before (Pre-MST) and after (Post-MST) the treatment. Before the training, movements of the paretic hand were associated with bilateral motor activations that were reduced after the training, showing a pattern of intrahemispheric reorganisation within the lesioned hemisphere. Adapted from Ripollés et al., 2015.

The results of this study indicate that i) the role of the auditory feedback in training might be critical in restoring the audio-motor network and ii) Music-supported Therapy can induce a pattern of intrahemispheric reorganisation within the lesioned hemisphere.

Regarding the role of the auditory feedback, a study comparing Music-supported Therapy to a mute version of the training showed that stroke patients improved more when the auditory feedback was provided (Tong et al., 2015). In an interesting study, Van Vugt and colleagues (2016) manipulated the presentation of the auditory feedback during the training with Music-supported Therapy (Van Vugt et al., 2016). In the experimental group, the feedback was delayed (from 100 to 600 ms) whereas in the control group patients received immediate auditory feedback while playing. The results of this study showed that both groups improved their motor function, but patients who received delayed feedback improved substantially. Authors concluded that coupled feedback might serve to overcorrect for errors, and therefore delayed feedback could be beneficial since it would disrupt the online integration of the movement outcome (Van Vugt et al., 2016). However, it could also be that a subtle delay of auditory information increases patient's expectations and movement outcome awareness. In a similar vein, playing in turns might improve the functional use of the affected upper extremity more than playing in pairs (Van Vugt, Ritter, Rollnik, & Altenmüller, 2014). The sound of the instrument in Music-supported Therapy provides sensory information that seems to be beneficial for motor learning and audio-motor coupling restoration.

About the plastic changes within the lesioned hemisphere promoted by Music-supported Therapy, Amengual and colleagues (2013) reported an increase in the excitability and a cortical

motor map reorganisation in the affected sensorimotor cortex of chronic stroke patients after training (Amengual et al., 2013). However, in this study, the lack of a control group of patients undergoing a different therapy is a limitation when concluding that these changes were specific to the treatment. As previously described, other types of motor therapies can promote similar cortical representation changes (Classen et al., 2014; Joachim Liepert, Bauder, Miltner, Taub, & Weiller, 2000).

Music-supported Therapy not only comprises complex and coordinated movements but also entails demanding cognitive functioning. The complex association between movements and sounds might lead to increased attentional levels and cognitive control since patients have to select relevant cues and plan an appropriate response. Verbal learning has been shown to improve after Music-supported Therapy in chronic patients (Ripollés et al., 2016), probably because the processing of relevant features of music such as rhythm and beat share several networks with language processing (Patel, 2011). Moreover, patients treated with Music-supported Therapy have reported increased quality of life and positive emotions as well as a reduction of fatigue and depressive symptoms (Ripollés et al., 2016; Van Vugt, Ritter, Rollnik, & Altenmüller, 2014).

As an interim conclusion, Music-supported Therapy is a therapeutic neurorehabilitation intervention that seems effective in enhancing the functionality of the paretic upper extremity in subacute and chronic stroke patients (Ripollés et al., 2016; Schneider et al., 2007). Moreover, Music-supported Therapy can increase verbal memory, promote positive affect, reduce depressive symptoms and improve quality of life in stroke patients (Ripollés et al., 2016). Furthermore, it can induce intrahemispheric reorganisation within the lesioned hemisphere, with changes in the excitability of the sensorimotor cortex, cortical motor map reorganisation and audio-motor coupling restoration in chronic stroke patients (Amengual et al., 2013; Ripollés et al., 2016; Rodriguez-Fornells et al., 2012).

1.3.2.2 Music glove

Music glove aims to facilitate the practice of movements with the affected extremity at home (Friedman et al., 2014; Zondervan et al., 2016). This device consists of a glove that produces different sounds when gripping and pinching movements are performed and challenges patients with an interactive computer game to play along with songs. When compared to self-guided hand exercises, two RCTs in the chronic phase have led to different results, one pointing out that the effects of Music glove were superior to self-guided hand exercises (Friedman et al., 2014) and the other one showing no treatment superiority (Zondervan et al., 2016).

1.3.2.3 Classical approaches to music therapy

Classical approaches to music therapy are different from other types of music-based interventions such as Music-supported Therapy or Music glove. Sessions are less structured, have a special focus on the relational and emotional aspects, and are conducted by a music therapist. These therapies could be feasible and motivating for stroke patients (Street et al., 2018). In Music upper limb therapy-integrated, stroke patients are engaged in group sessions of interactive live music making (Raghavan et al., 2016). Together with the music therapist, patients improvise music with different adapted musical instruments. The instruments include maracas, drums, and piano among others that are selected based on the patient's preferences, abilities and motor deficits. In Music upper limb therapy-integrated, specific attention is paid to offer a successful and personally fulfilled experience to the patients. It also aims to facilitate emotional expression through the selection of the type of music, interpersonal communication, and a sense of belonging to the group. A study of thirteen chronic stroke patients undergoing this treatment has shown that patients reduced their motor and sensory deficits, and increased their functionality, well-being and participation (Raghavan et al., 2016). In a similar vein, active music therapy approach involves social, communicative and relational aspects in group music playing. Raglio and colleagues (2017) have observed that adding music therapy to a standard program of rehabilitation for subacute patients can increase grip strength. Patients also improved their quality of life, functional level and gross mobility although these improvements were also seen in the control group who received the standard program of rehabilitation alone (Raglio et al., 2017).

1.3.2.4 Moving to the music and moving to create music

Moving according to the music and making music through movements have also been used as a form to recover motor deficits after stroke. An example of the former is Rhythm- and music-based intervention, which is a multi-sensory stimulation therapy based on the Ronnie Gardiner Rhythm and Music method (RGRM™) developed by jazz drummer Ronnie Gardiner (Bunketorp Käll et al., 2012). In this method, a note system with visual cues of different symbols and colours is used to prompt movements of the right and left hand and foot. Movements include clapping hands, tapping hands on knees, and stamping the feet on the floor. Using music as a background, the therapist displaces the cues on a screen to move to the music. The difficulty of movement sequences is adapted to the level of mobility and is increased in complexity throughout sessions. In a RCT, Bunketörp-Käll and colleagues (2017) compared the effects of Rhythm- and music-based therapy to horse riding and no treatment in chronic stroke patients (Bunketorp-Käll,

Lundgren-Nilsson, Samuelsson, et al., 2017). Patients treated with Rhythm- and music-based therapy reported a greater perception of recovery, and improved in balance, grip strength and working memory when compared to patients who did not receive any treatment. Importantly, patients in the horse-riding group also increased their perception of recovery and improved in gait and balance. In both active treatment groups, behavioural improvements were maintained over time, and caregiver burden was reduced (Bunketorp-Käll, Lundgren-Nilsson, Nilsson, & Blomstrand, 2017; Bunketorp-Käll, Lundgren-Nilsson, Samuelsson, et al., 2017).

Training through Musical sonification therapy has been used to enhance gross movements of the upper extremity in the early subacute phase of stroke recovery (Scholz et al., 2016). During the sessions, patients are seated at a desk with a three-dimensional space frame, and when they move their upper extremities forward, upward or to the left or right, sounds are produced with variations in scale, volume and type of instrument. Although patients need some time to familiarise with the training setting through implicit learning, once they are aware of the rules of Musical sonification therapy, they are encouraged to perform exercises that increase in complexity. In a RCT comparing Musical sonification therapy to the same exercises in a mute version, this therapy was not superior since the functional use of the affected extremity was enhanced in the silent condition as well but patients who listened to the music experienced a reduction in pain after the training (Scholz et al., 2016).

1.3.3 Clinical questions

Despite the growing number of studies validating music-based interventions to treat upper extremity motor function in stroke, there is still the need to replicate results, conduct larger trials and multicentre studies. A recent systematic review of music interventions concluded that the majority of studies have a high risk of bias and more high-quality RCTs are needed before accepting music-based interventions into clinical practice guidelines (Magee, Clark, Tamplin, & Bradt, 2017). Importantly, pooling the results should be done with caution since the protocols of training differ among different types of therapies, and the underlying mechanisms supporting the effectiveness of these therapies might be different as well.

In the case of Music-supported Therapy, there are relevant clinical questions that should be addressed to understand the effectiveness of this therapy better. In all the studies presented in Table 7 investigating Music-supported Therapy, the primary outcome has been the motor function of the paretic upper extremity. This means that stroke patients have been evaluated regarding the activity level of the ICF framework, but the effects of the therapy in reducing the motor impairment of the upper extremity have not been explored. Moreover, when previous

studies have evaluated the functionality of the paretic upper extremity, the standardised motor function tests that have been used only comprise simple motor tasks (i.e. manipulating wooden blocks or sticks). Thus, it is unclear if improvements in motor function are generalised to movements required in activities of daily living such as picking up the phone or using a fork while eating. Also, none of these studies has explored how the patient's musical task performance improves during the training. The time course of motor gains throughout the training phase is unknown as well as if motor improvements are maintained over time.

One important aspect in any rehabilitative intervention is the motivation of the patient towards the task. It could be that patients who enjoy musical activities more may show a major enhancement at the motor level when treated with Music-supported Therapy, but no previous study has addressed this issue.

Regarding the neuroplastic mechanisms associated with Music-supported Therapy, these have only been investigated at the chronic stage, in an experimental study that did not have a control group of patients receiving a different treatment (Amengual et al., 2013; Ripollés et al., 2016). Therefore, it is unknown which are the plastic changes specifically induced by Music-supported Therapy in the subacute stage and when compared with conventional treatment. Further research is needed to elucidate the underlying mechanisms behind the effectiveness of Music-supported Therapy. Similarly, we only have evidence of the effects of Music-supported Therapy on cognition and on improving the mood and quality of life of patients that is derived from this same experimental study. Thus, no direct comparison has been made between Music-supported Therapy and any other type of therapy on enhancing these cognitive and emotional domains. Furthermore, there has been no previous study addressing the question of adequate dose-response of Music-supported Therapy.

Research aims

Chapter 2. Research aims

The main aim of this thesis was to study the effectiveness of Music-supported Therapy as a treatment in the rehabilitation of upper extremity motor function after stroke. Using different study designs, we have investigated the effects of Music-supported Therapy in enhancing different levels of functionality in stroke patients, with measurements at the neural, body functions, activity and participation level.

2.1 Study 1

The first study of this thesis was designed to test the effectiveness of Music-supported Therapy in treating the hemiparesis of the upper extremity, inducing neuroplastic changes in the sensorimotor cortex, and improving the quality of life in subacute stroke patients.

An interventional experimental design was used where a group of subacute stroke patients received four weeks of Music-supported Therapy in addition to the standard rehabilitation program. Participants were assessed before and after the treatment in an evaluation that was focused on three domains. Firstly, the motor ability of patients in performing functional tasks was assessed using standardised clinical motor tests. Secondly, the mechanisms of brain plasticity were investigated using Transcranial Magnetic Stimulation, which allows the study of changes in the excitability of the sensorimotor cortex as well as cortical motor map reorganisation. Thirdly, a quality of life questionnaire was used to evaluate the patients' perception of their quality of life. A healthy group of matched controls was also evaluated to rule out the explanation that the changes observed in the patients' group were because of an effect of time between evaluations.

We hypothesised that Music-supported Therapy would improve the motor ability of the paretic upper extremity in subacute stroke patients and that these improvements would be accompanied by plastic changes in the sensorimotor cortex after the training. Moreover, we hypothesised that patients would improve their quality of life after Music-supported Therapy.

2.2 Study 2

Study 2 is a RCT designed to test the effectiveness of Music-supported Therapy as an add-on treatment in the rehabilitation of the upper extremity hemiparesis after stroke compared with conventional therapy.

In this study, subacute stroke patients were randomised into two groups of treatment: a group receiving a four-week program of Music-supported Therapy or a group that received extra time of conventional therapy. Participants in both groups were undergoing a standard rehabilitation program that included physiotherapy, occupational and speech therapy. Thus, this study evaluated Music-supported Therapy as an add-on treatment, aimed at complementing the standard rehabilitation program. Before and after the four-week treatment, participants were evaluated on these domains: motor functions, cognitive functions, and mood and quality of life. A follow-up evaluation at three months was conducted to examine the retention of motor gains.

At the motor level, this study offers four innovative perspectives: if Music-supported Therapy reduces the motor impairment, whether motor improvements are generalised to activities of daily living, which is the retention of motor gains over time and if musical reward is associated to motor improvements.

We hypothesised that Music-supported Therapy would improve the motor ability and reduce the motor impairment of the paretic upper extremity in stroke patients and that these improvements would be greater when compared with conventional therapy. Moreover, if Music-supported Therapy can lead to enhancing the overall motor function in stroke patients; these motor gains would be evidenced in the performance of everyday tasks. We also hypothesised that the patients' individual differences in their capacity to experience pleasure from musical activities would be associated with motor improvements in the Music-supported Therapy group. At the cognitive and emotional level, our hypotheses were that patients would show an enhancement in cognitive functions, and would improve their mood and quality of life after the treatment with Music-supported Therapy.

2.3 Study 3

This study aimed to characterise the lesions and white matter damage of patients, study the relationship between the integrity of the corticospinal tract and motor improvement and investigate the mechanisms of brain plasticity associated with Music-supported Therapy compared with conventional treatment in subacute stroke patients.

A subsample of Study 2, where Music-supported Therapy was compared to conventional therapy, was evaluated using structural and functional Magnetic Resonance Imaging before and after the intervention. To characterise the patients' lesion, structural images were used to draw lesion masks. These masks also served to analyse the proportion of disconnection of relevant frontal tracts. A finger tapping task was used to evaluate functional changes and reorganisation after Music-supported Therapy compared to conventional therapy.

Our hypothesis were that the integrity of the corticospinal tract was related to motor improvements and that patients treated with Music-supported Therapy would show a pattern of intrahemispheric reorganisation within the lesioned hemisphere.

2.4 Study 4

In Study 4, we evaluated a chronic stroke patient treated with Music-supported Therapy using a single-case design to explore the progression of motor improvements throughout the training sessions and examine the effects of a second period of training. Moreover, we wanted to study the retention of motor gains over time and investigate the generalisation of motor improvements on activities of daily living.

This single-case study made use of a reversal ABAB design, where no treatment was provided in the A periods, and a four-week program of Music-supported Therapy was applied during the B periods. Each week, a motor evaluation and three-dimensional (3D) movement analysis were performed to examine the motor function of the paretic upper extremity. Moreover, the patient's musical task performance was assessed after each training session. The study design included a follow-up evaluation three months after completing the second period of training.

For the first time improvements in instrument playing were examined during the progression of the treatment. This evaluation, together with the patient's continuous clinical assessment during the periods of training and rest, gave us the possibility of studying when motor improvements occurred throughout the training sessions, and which was the retention of these gains when there was no treatment. Overall, this type of design might provide insight into the most optimal protocol regarding time.

In this study, we hypothesised that gains in playing-related movements would show a different temporal trajectory, with rapid improvements during the first training sessions, than general motor skills in a chronic stroke patient treated with Music-supported Therapy. We also hypothesised that a second period of Music-supported Therapy would be important to enhance functional gains. Furthermore, we expected that improvements of the upper extremity motor function would be maintained over time and that transference of motor improvements to activities of daily living would occur at the end of the training.

2.5 Summary of studies

Each of the four studies investigated different aspects regarding the effectiveness of Music-supported Therapy. In Table 1, specific aims are presented by studies and

Chapter 2. Research aims

Table 2 summarises the methodology of each study with regard to the study design, sample, treatment and evaluations.

Table 1. Specific aims by studies.

Specific aims	Study 1	Study 2	Study 3	Study 4
To investigate the effectiveness of Music-supported Therapy in enhancing motor ability and restoring motor deficits of the upper extremity in stroke patients.	•	•		•
To investigate the generalisation of upper extremity motor gains induced by Music-supported Therapy on activities of daily living in stroke patients.		•		•
To explore the long-term retention of upper extremity motor gains promoted by Music-supported Therapy in stroke patients.		•		•
To explore the relationship between the patients' capacity to experience pleasure in musical activities and the motor gains induced by Music-supported Therapy.		•		
To study the mechanisms of brain plasticity associated with Music-supported Therapy in stroke patients.	•		•	
To investigate the effects of Music-supported Therapy on enhancing the cognitive function of stroke patients.		•		
To investigate the effects of Music-supported Therapy on improving the mood and quality of life of stroke patients.	•	•		
To investigate the dose-response of a program of Music-supported Therapy to treat motor deficits in stroke patients.				•

Specific aims are presented and dots indicate in which of the four studies the aim is addressed.

Chapter 2. Research aims

Table 2. Summary of the methodology of each study.

	Study 1	Study 2	Study 3	Study 4
Study design	Experimental study	RCT	RCT	Single-case ABAB
Recovery phase	Subacute	Subacute	Subacute	Chronic
Participants (n)				
Experimental group	9 stroke patients	20 stroke patients	Subsample of Study 2	1 stroke patient
Music-supported Therapy			14 stroke patients	
Control group	9 healthy participants	20 stroke patients	Subsample of Study 2	None
			15 stroke patients	
Control treatment	None	Conventional therapy	Conventional therapy	None
Duration of interventions	4 weeks 20 sessions 30 min each session	4 weeks 20 sessions 30 min each session	4 weeks 20 sessions 30 min each session	4 weeks 12 session 1 h 30 min each session
Evaluation time points	Pre-intervention Post-intervention	Pre-intervention Post-intervention Follow-up 3 months	Pre-intervention Post-intervention	Each week Follow-up 3 months
Outcomes	Motor function Brain plasticity (TMS) Quality of life	Motor function and impairment Cognitive function Mood Quality of life	Brain plasticity (fMRI)	Motor function and impairment 3D movement analysis Musical task performance

The study design, sample, treatment and evaluation is presented for each study. In Study 4, ABAB refers to 4 phases where no treatment was provided in the A periods and Music-supported Therapy was administered in the B periods. TMS, Transcranial Magnetic Stimulation; RCT, Randomised Controlled Trial; fMRI, functional Magnetic Resonance Imaging; 3D movement analysis, Three-dimensional movement analysis.

Study 1

Chapter 3. Study 1

Plasticity in the sensorimotor cortex induced by Music-supported Therapy in stroke patients: a Transcranial Magnetic Stimulation study¹

3.1 Introduction

Stroke represents a major cause of death and the most important cause of acquired disability in adults from developed countries (World Health Organization, 2003). In stroke survivors, motor deficits are present in a majority of patients (Rathore et al., 2002), leading to limitations in the participation of activities of daily living and preventing patients to live independently. For this reason, restoration of motor deficits is the target of many different therapies (Langhorne et al., 2011).

Usually, the rehabilitation process of motor impairments comprises different stages. In the beginning, motor function is assessed through domain-specific measures in order to set goals with the patient. Subsequently, therapeutic interventions are provided and, finally, reassessment is performed to ensure that motor improvements have been achieved. In practice, this process is not always evidence-based but many times guided by the practitioner's expertise. Thus, there is a necessity to investigate effective motor rehabilitation therapies to provide evidence for clinicians (Cramer et al., 2011; Langhorne et al., 2011; Taub et al., 2002).

Besides their clinical efficacy, rehabilitation techniques may be validated by evidence for neuroplasticity which is defined as the capacity of the central nervous system to reorganize its structure, function and connections in response to internal and external constraints and goals during learning, development or after injury (Cramer et al., 2011; Kolb & Whishaw, 1998). Neuroplasticity may be induced due to therapy as behaviour can lead to a reorganisation of representational maps (Muellbacher et al., 2002; Nudo et al., 1996) as well as intra- and

¹ The results presented in this chapter correspond to:

Grau-Sánchez, J., Amengual, J. L., Rojo, N., Veciana de las Heras, M., Montero, J., Rubio, F., ... & Rodríguez-Fornells, A. (2013). Plasticity in the sensorimotor cortex induced by Music-supported therapy in stroke patients: a TMS study. *Frontiers in human neuroscience*, 7, 494.

interhemispheric changes and balance (Chollet et al., 1991; Grefkes et al., 2008; Murase et al., 2004).

One of the most studied rehabilitation techniques is the constraint-induced movement therapy (Taub et al., 1993), which comprises the forced use of the paretic extremity for many hours a day by restricting movement of the healthy extremity in combination with shaping techniques. Studies in subacute and chronic patients have shown improvements in motor function that are accompanied with reorganisation of cortical motor regions evidenced by Transcranial Magnetic Stimulation (TMS, Liepert et al., 1998; Taub et al., 1993). For example, Liepert and colleagues (2000) reported an expansion of the contralateral cortical area responsible for arm movements after the application of constraint-induced movement therapy (Liepert et al., 2000). It has been suggested that the success of this therapy may rely on the repetitive massed practice of movements performed with the affected extremity overcoming its learned non-use. Notice that learning processes feature prominently not only in neurorehabilitation (Krakauer, 2006) but also in the development of the motor deficits themselves. For example, patients with a motor deficit of the right hand will learn to perform movements predominantly with the (usually non-dominant) left hand. At the same time, this may lead to additionally learned non-use of the right hand. It is important to develop new therapeutic strategies to overcome the learned non-use of the affected side, paying special attention to how to perform specific movements. A way to achieve this goal could be through techniques where there is specific training for patients in activities that could represent the acquisition of new motor skills that could promote brain plasticity (Dayan & Cohen, 2011). During motor skill learning, the massive practice of movements can reduce kinematic and dynamic execution errors (Doyon & Benali, 2005; Krakauer, Ghilardi, & Ghez, 1999). On the other hand, motor skill training will be more effective if task variability is introduced into the training program. These variations could be related to sensorial cues involved in the training (multimodality) which leads to dynamic sensorimotor readjustments and, consequently, internal motor control models can be created and generalised to other situations (Conditt, Gandolfo, & Mussa-Ivaldi, 1997). In this regard, it has been demonstrated that neuroplasticity could be observed at cortical and subcortical levels due to motor skill learning (Dayan & Cohen, 2011; Draganski et al., 2004; Nudo & Milliken, 1996; Penhune & Steele, 2011; Willingham, 2001).

One example of a skill involving movements of the hand is musical instrument playing. The presence of music during motor learning posits unique and complex demands for the central nervous system (Zatorre et al., 2007), as playing an instrument requires the integration of multimodal information (auditory, visual, and sensorimotor information, Pantev & Herholz, 2011). During music performance, there are feedback and feedforward interactions between the

auditory and premotor areas of the cortex. As in other motor skills, motor, premotor, supplementary motor area, the cerebellum and the basal ganglia are involved in musical motor performance (Lotze, Scheler, Tan, Braun, & Birbaumer, 2003; Meister et al., 2004). In addition, the sound of the instrument processed by the auditory cortex can be used to readjust movements leading to interactions between the auditory and motor systems (Zatorre et al., 2007). Compared to other sensorimotor activities, music learning involves the integrated activity of motor and auditory systems. Furthermore, because of the consequent and consistent auditory feedback (Zatorre, 2003), correction of errors in timing, strength and position of the movement is possible. Studies with functional Magnetic Resonance Imaging (fMRI) exploring professional musicians and non-musicians have demonstrated that musical training leads to structural and functional changes in motor regions of the brain, especially those involving auditory and sensorimotor cerebral networks (Bangert et al., 2006; Baumann et al., 2007; Bengtsson et al., 2005; Gaser & Schlaug, 2003; Herholz & Zatorre, 2012; Hyde et al., 2009; Steele, Bailey, Zatorre, & Penhune, 2013). For instance, in healthy subjects, motor cortex was explored with TMS when participants were trained to play the piano showing an enlargement of the cortical representation of the hand after the training (Pascual-Leone et al., 1995). Therefore, learning to play the piano is an example of a music making activity that requires repetitive massed practice and entails variations in the training task (i.e., movement sequences), involving complex coordination. Moreover, playing the piano engages different regions of the brain and could be associated with structural and functional brain changes. Beyond the plasticity in motor regions associated to music making, studies investigating the effects of music listening as a rehabilitative intervention have revealed improvements in cognition and emotional factors (Särkämö & Soto, 2012; Särkämö et al., 2008). These findings add value to the interventions based on motor learning using music making because of their possible impact on other cognitive and emotional domains aside from the expected motor improvements.

Recently, Schneider and colleagues (2007) have developed Music-supported Therapy to restore motor function after stroke. In this therapy, patients are trained to play a MIDI piano and an electronic drum set that produces piano tones, involving fine and gross movements, respectively (Schneider et al., 2007). Music-supported Therapy has been tested in stroke patients showing improvements in the execution of movements revealed by an increase in the scores of behavioural motor tests after the application of Music-supported Therapy (Altenmüller et al., 2009; Schneider et al., 2007). A recent study about a single chronic stroke patient showed that Music-supported Therapy can lead to improvements in motor function after 2 years since the stroke. Gains in motor function were accompanied by changes in motor cortex excitability (evaluated using motor mapping TMS) with an expansion of the cortical representation of the hand and by activation changes in fMRI (Rodriguez-Fornells et al., 2012; Rojo et al., 2011). In

addition, Amengual and colleagues (2013) have reported evidence from a group of chronic patients that have been treated with Music-supported Therapy (Amengual et al., 2013). Patients improved their motor function and an increase in the excitability of the motor system was encountered. Moreover, gains in motor performance were correlated with changes in the cortical representation of a muscle of the paretic hand.

In the present study, Music-supported Therapy was administered to stroke patients with hemiparesis of the upper limb to restore their motor function. Thus, the aim of the present study is to investigate improvements in motor function in subacute stroke patients and whether this restoration is accompanied by neuroplastic changes in the sensorimotor cortex. Moreover, we wanted to test the effectiveness of Music-supported Therapy in improving the quality of life of subacute stroke patients.

3.2 Methodology

3.2.1 Participants

Nine right-handed stroke patients with impairment of the motor function of one arm following a stroke participated (3 women, mean age 61.8 ± 9.8 years, years of education 10.8 ± 8). Inclusion criteria were: (i) less than 6 months after stroke, (ii) mild-to-moderate paresis of upper extremity, (iii) ability to move the affected arm and the index finger without help of the healthy side, (iv) Barthel Index score over 50, (v) no major cognitive deficit, (vi) no neurological or psychiatric co-morbidity. Table 1 presents individual demographic data and Figure 1 illustrates the lesion for each patient.

Besides, a matched sample of 9 healthy participants (2 women, mean age 59.3 ± 9.5 years, education 12.2 ± 7 years) composed the control group. Participants in this group were right-handed and without any history of stroke or other neurological or psychiatric disease. They were evaluated in two different time points in order to control repeated imaging testing effects (Johansen-Berg, 2012) and did not receive any training between evaluations.

The study was approved by the committee of ethics for clinical research of the Hospital Universitari de Bellvitge and fulfilled the standards set by the Declaration of Helsinki. All participants signed an informed consent form explaining the purpose of the study and all procedures.

Chapter 3. Study 1

Table 1. Clinical description of participants.

Participant	Age	Gender*	Affected hemisphere*	Aetiology*	Localization of stroke	Time since stroke (months)	MRCS* Pre	Barthel Index
1	72	M	R	I	Putamen, globus pallidus and partial damage to the head and body of the caudate nucleus. Anterior and superior portion of the anterior limb of the internal capsule and corona radiata.	3	5-	80
2	63	F	R	I	Lenticular nucleus, body of the caudate nucleus and corona radiata.	2	4-	70
3	59	M	L	I	Cortical and subcortical parietal regions (extreme portion of the superior postcentral gyrus) slightly extended to the surrounding white matter.	1	5-	100
4	63	M	R	H	Lenticular nucleus, internal and external capsule and deep temporal regions.	2	4	100
5	52	M	L	I	External capsule	2.5	4+	100
6	68	M	R	I	Subcortical damage located in paraventricular regions and semioval center.	4.5	3	100
7	76	F	R	I	Extensive cortical damage to frontotemporoinular regions extended to subcortical areas including the semioval centre and corona radiata.	4	4	60
8	60	F	R	I	Anterior frontal cortex, basal ganglia including the body of the caudate nucleus and the capsular-lenticular region.	5	4	100
9	44	M	R	I	Frontal regions comprising the inferior extreme of the lateral fissure and the superior precentral gyrus.	2.5	4+	100
Mean (SD)	61.8 (9.8)	6M/3F	7R/2L	8I/1H		2.9 (1.3)	4.1 (0.6)	88.8 (16.7)

*M, male; F, female; R, right; L, left; I, ischaemic; H, haemorrhagic; MRCS, Medical Research Council Scale for Muscle Strength.

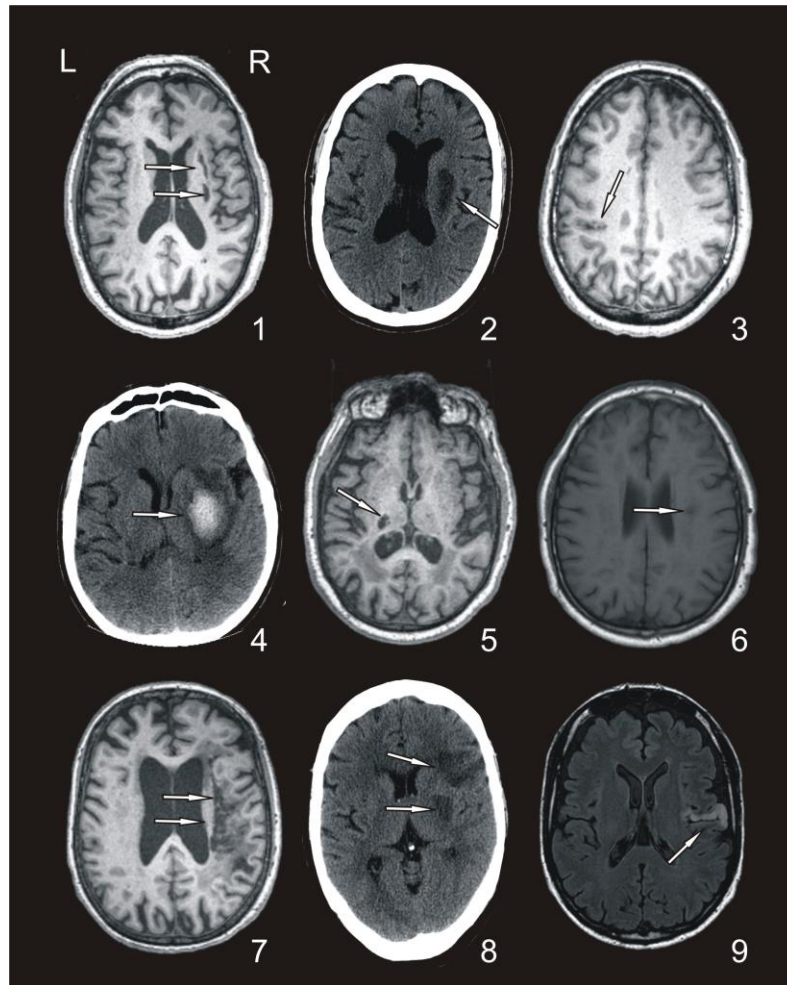


Figure 1. Location of participants' lesions.

Representative axial Magnetic Resonance and Computed Tomography images of the patients. Arrows show the approximate location of each lesion (patient codes are according to the order in Table 1).

3.2.2 Music-supported Therapy

During four weeks, patients received 20 individual Music-supported Therapy sessions of 30 minutes each. A MIDI-piano and an electronic drum set were used to train fine and gross movements, respectively. For the MIDI-piano, only 8 white keys (G, A, B, C, D, E, F, G') were used, whereas the electronic drum set comprised 8 pads of 20 cm diameter designated by the numbers 1 - 8 and programmed to emit piano sounds. During the different sessions, patients had to produce tones, scales and play some simple melodies according to a modular training regime with a stepwise increase of complexity (Schneider et al., 2007). Exercises were adapted to the needs of the individual patient in difficulty and were first shown by the therapist.

3.2.3 Evaluation

Before and after the Music-supported Therapy program, patients were evaluated with regard to their motor function and quality of life. In addition, TMS was performed. Participants in the control group underwent the same evaluation as patients but were not evaluated for quality of life. The second evaluation of the control participants was done between 30 and 40 days after the first assessment.

3.2.3.1 Evaluation of motor function

Motor function was assessed using the Action Research Arm Test (ARAT), Arm Paresis Score (APS), Box and Blocks Test (BBT) and the Nine Hole pegboard Test (9HPT):

(i) ARAT: Patients are assessed for different movements of both upper extremities within four subtests: grasp, grip, pinch, and gross movement which are composed by different items. Scores describe the quality of movement execution with the maximum score being 57 (Carroll, 1965; Lyle, 1981).

(ii) APS: Patients are asked to perform 7 movements with either the affected hand or both hands. The maximum score is 7 (Wade, Langton-Hewer, Wood, Skilbeck, & Ismail, 1983).

(iii) BBT: In this test, patients have to move as many small cubes placed in one compartment of a box to a second compartment within 1 minute. The number of moved cubes is scored (Mathiowetz, Volland, Kashman, & Weber, 1985).

(iv) 9HPT: Patients are asked to place 9 rods (32 mm long, 9 mm diameter) into holes of 10 mm diameter. Scores are given depending on the time needed to accomplish the task (Parker, Wade, & Langton Hewer, 1986).

3.2.3.2 Evaluation of quality of life

The Stroke-specific Quality of Life Scale (Williams, Weinberger, Harris, Clark, & Biller, 1999), which is a disease-specific measure of health-related quality of life, was administered to test if Music-supported Therapy improved the quality of life of patients. It comprises 12 domains evaluating energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision and productivity. Each domain contains different items asking the patient the amount of help required, trouble experienced doing tasks, and the degree of agreement with statements about functioning. The minimum/maximum possible scores are 49/245.

3.2.3.3 Evaluation of cortical excitability

TMS was applied using a 70 mm figure-of-8 coil attached to a Magstim Rapid 2 Stimulator (Magstim Company, Carmathenshire, Wales). The primary motor cortex was stimulated in a single pulse protocol to elicit motor-evoked potentials (MEPs) from the first dorsal interosseous (FDI). Using surface Ag/AgCl disk electrodes in a belly-tendon montage, electromyographic (EMG) activity from the contralateral FDI was recorded for a total of 700 ms including a 100 ms pre-stimulus window (Medelec Synergy, Oxford Instruments, Pleasantville, NY, USA). The EMG signal was sampled at 5 KHz and band-pass filtered at 1 - 1000 Hz. Data was exported for off-line analysis using specialised software (Matlab, Mathworks, Natick, MA, USA).

To allow simple identification of stimulation sites, participants wore an elastic cap in which Cz location was marked (international 10/20 EEG positioning system). A grid of 10 × 10 spots was drawn (Cz was centred in the vertex), and the difference from one spot to the other was 1 cm. In this grid, there were two perpendicular axes where the *x*-axis is horizontal, and the *y*-axis is vertical (two-dimensional, Cartesian coordinate system). Stimulation sites were defined following *x* and *y*-axes and becoming coordinates (*x,y*) in the grid (Amengual et al., 2013).

To increase the between-session reliability, a single cap was used per participant in both evaluations. The TMS coil was placed tangentially to the corresponding grid location, with the handle pointing backwards (in a lateral to medial and caudal to rostral position) ~45° lateral from the midline.

Both hemispheres were tested to assess the excitability of the corticospinal pathway using the following parameters: coordinates of Hot Spot, resting motor threshold (RMT), active motor threshold (AMT, Rossini et al., 1994), cortical silent period (CSP, Liepert, Restemeyer, Kucinski, Zittel, & Weiller, 2005), peak-to-peak amplitude, motor map area and volume, and the coordinates of the centre of gravity of the map (CoG_{*x*} and CoG_{*y*}, Amengual et al., 2013, 2012; Byrnes, Thickbroom, Phillips, Wilson, & Mastaglia, 1999; Wassermann, McShane, Hallett, & Cohen, 1992). Below, a further description of each parameter is provided for better understanding.

The Hot Spot is defined by the coordinates yielding the highest MEP in the target muscle. RMT is defined as the lowest stimulus intensity needed to evoke a visible MEP (>50 μV) in 50% of 10 trials from the relaxed target muscle. On the other hand, AMT is defined as the minimum stimulus intensity that produces a visible MEP (>200 μV) in 50% of 10 trials during isometric contraction of the target muscle (Rossini et al., 1994). RMT and AMT are expressed in percentage of maximum stimulation intensity.

The CSP is defined as an interruption of voluntary muscle contraction in response to a TMS pulse (Hallett, 2007). CSP is obtained by applying a suprathreshold TMS pulse (150% of RMT) when the target muscle is preactivated at 10% of its maximum voluntary strength. The EMG typically shows suppression of the muscle activity, which lasts between 100 and 300 ms in healthy subjects. Cortical inhibition is thought to be responsible for the generation of the CSP but spinal inhibitory mechanisms may contribute to the first part of the CSP (Wassermann et al., 2008). The end of the CSP, defined as a return of EMG activity to baseline, is measured in ms.

MEPs peak-to-peak amplitudes, expressed in μV , were obtained at the Hot Spot as the mean of 5 consecutive stimulations at 125% of RMT (Rossini et al., 1994).

To obtain a motor map of the FDI, we recorded 5 MEPs from each different position in the grid at 125% of RMT. The map was generated by plotting peak-to-peak MEP amplitudes at each grid location (Byrnes et al., 1999; Wilson, Thickbroom, & Mastaglia, 1993). The area of the map was considered as the number of excitable scalp points (Liepert et al., 1998). As the difference between each spot in the grid was 1 cm, each active spot (MEPs > 50 μV) was accounted as 1 cm^2 of the area of the motor map. The volume of the map was calculated dividing the sum of the amplitudes of the motor map by the area of the map ($\mu\text{V}/\text{cm}^2$). The centre of gravity (CoG) was considered as the amplitude-weighted coordinates of the map (Wassermann et al., 1992). The coordinates of the CoG, named CoG_x and CoG_y , indicate the position of the spot in the horizontal x -axis and the vertical y -axis of the grid.

Unfortunately, 3 patients were not eligible for TMS because of severe heart disease (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009).

3.2.4 Analysis

Each patient was paired with a control participant. The control participant's hemisphere corresponding to the affected hemisphere of the patient was considered for comparison. Thus, the hemisphere that is considered as affected in controls is the right with the exception of controls for Patients 1 and 5 who have their lesion in the left hemisphere. Then, for these two controls, the hemisphere that is considered as the affected is the left. We performed an exploratory analysis across all parameters in order to identify which TMS variables showed an interactive effect between Group (patients and controls). We used non-parametric tests due to the reduced sample size. To this aim, we computed the difference between both evaluations (Post-Music-supported Therapy evaluation minus Pre-Music-supported Therapy evaluation) for each parameter and applied the Mann-Whitney U -test between controls and patients to this difference. The rationale behind this analysis is that only those measures that are affected or

sensitive to the treatment will show differences between groups. Notice that this type of analysis was not carried out for the motor performance measures due to the ceiling effects of the control group in these measures. For the motor assessment and when we found differences between groups in TMS parameters, we measured the significance of change between pre-Music-supported Therapy and post-Music-supported Therapy evaluation using the Wilcoxon signed-rank test. The statistical significance was set to 0.05. Finally, we computed the magnitude of the effect size (r) using the criteria stated by Cohen (1992), where a value of 0.10 is a small effect, a value of 0.30 is a medium effect, and 0.50 is a large effect.

3.3 Results

3.3.1 Evaluation of motor function

Results for the ARAT, APS, BBT and 9HPT are summarized in Table 2. As participants in the control group showed maximal scores at the first evaluation, no improvement can be found in this group. In patients, significant improvements were found for the ARAT overall score ($T = 0, p = 0.008, r = -0.62$), the APS ($T = 0, p = 0.038, r = -0.48$) and the BBT score ($T = 1.5, p = 0.012, r = -0.58$). No differences were observed between pre- and post-Music-supported Therapy in the 9HPT score.

Table 2. Results of the clinical motor tests (Mean, SD).

Motor test	Patients		Controls	
	Pre-MST	Post-MST	Pre	Post
Action Research Arm Test ^{*b}	37.7 (21.8)	45.5(5.35)	57 (0)	57 (0)
Arm Paresis Score ^{*a}	5 (2.5)	5.7 (1.8)	7 (0)	7 (0)
Box and Blocks Test ^{*b}	28.4 (19.5)	33.7 (23.09)	62.2 (10)	68 (8.6)
Nine Hole Pegboard Test	4.7 (4.1)	4.7 (3.8)	9 (0)	9 (0)

^aMedium to large effect size; ^bLarge effect size; MST, Music-supported Therapy; * $p < 0.05$.

3.3.2 Evaluation of quality of life

In patients the score of the Stroke-specific Quality of Life Scale improved from 160 (± 32.5) to 194 (± 38.2) ($T = 5, p = 0.038, r = -0.48$).

3.3.3 Evaluation of cortical excitability

As stated above, only six patients were assessed in the TMS evaluation. In addition, during the pre-therapy evaluation, one subject did not show MEP responses for the FDI of the affected hand. However, MEP responses for this muscle were observed after the therapy. Consequently, only motor thresholds were considered for this subject as a dependent variable of the affected hemisphere for the statistical analysis. It was not possible to perform the rest of the measurements in this subject. Table 3 shows the values of the parameters assessed in each group and hemisphere across time.

Table 3. Results of the TMS measures (Mean/SD).

TMS measure	Affected Hemisphere				Unaffected Hemisphere			
	Patients		Controls		Patients		Controls	
	Pre-MST	Post-MST	Pre	Post	Pre-MST	Post-MST	Pre	Post
RMT	69.5 (17.6)	66.8 (15.7)	70.7 (12.6)	71.6 (10.9)	54.3 (13)	56.1 (15.1)	66 (12.1)	68 (10.6)
AMT	62.1 (20.3)	56.1 (15.1)	53.4 (11.7)	55.4 (11.5)	46.3 (9.7)	44 (10.6)	48.6 (11.7)	50 (9.4)
CSP	306 (168.3)	377 (185.6)	212.3 (59.6)	219.8 (51.9)	217.3 (62.1)	215.5 (59.2)	232.8 (55)	241.6 (46.3)
MEPs peak-to-peak amplitude	389.4 (238.4)	361.8 (296.7)	1161.2 (919.6)	996.6 (876)	870.8 (786.8)	1114.8 (1321.2)	1102.5 (876)	1173 (1293.9)
Mapping area	18.4 (6.1)	20 (7.5)	18.8 (5.4)	15 (5.2)	15.3 (5.3)	16.3 (6.5)	15.7 (5.3)	16.1 (5.7)
Mapping volume	9.6 (4.8)	10.9 (5.9)	7.6 (1.7)	6.6 (1.9)	7 (2.4)	7 (3.7)	6.8 (1.8)	6.8 (2.3)
CoG_x	6.2 (1.4)	6.1 (1.3)	5.5 (.6)	5.2 (.4)	5.8 (.7)	5.8 (.6)	6.4 (.8)	6.4 (.9)
CoG_y	-1.6 (1)	-7 (1.1)	-1.6 (.6)	-1.6 (.4)	-1.2 (1.1)	-4 (1.1)	-1.6 (.6)	-1.6 (.4)

RMT, Resting motor threshold; AMT, active motor threshold; CSP, Cortical silent period; MEP, Motor-evoked potential; CoG, Center of gravity; MST, Music-supported Therapy. For the RMT and AMT values represent the intensity of stimulation (from 0 to 100%). The CSP is considered in ms and the MEP amplitude in μV . The area of the map is considered in cm^2 and volume in $\mu\text{V}/\text{cm}^2$. The CoG is expressed in coordinates (CoG_x for the x-axis and CoG_y for the y-axis).

A summary of the Mann-Whitney U -test comparing differences between groups in each parameter (measurements obtained subtracting post- minus pre-evaluation) is shown in Table 4.

Table 4. Between-groups comparisons of the TMS measures.

TMS measure	Affected Hemisphere			Unaffected Hemisphere		
	U	z	p	U	z	p
RMT	17.5	-1.12	.260	27	.00	1
AMT	7	-2.36	.018*	14	-1.54	.122
MEPs peak-to-peak amplitude	17	-.73	.463	21	-.70	.480
CSP	16.5	-.80	.423	20.5	-.26	.789
Mapping area	3	-2.61	.009*	10	-1.68	.092
Mapping volume	14	-1.13	.257	14	-1.13	.257
CoG _x	18	-.60	.544	18	-.60	.548
CoG _y	6	-2.20	.028*	7	-2.06	.039*

Significance of Mann-Whitney U test comparisons between groups for the TMS measurements obtained subtracting post- vs pre-treatment measurements. * $p < 0.05$.

We did not find any difference in RMT between groups and over time. However, we found a significant between-group difference in the change of the AMT of the affected hemisphere between both evaluations ($U = 7$, $z = -2.36$, $p = 0.018$, $r = -0.60$). Conversely, we did not find differences between both groups in the change of the AMT in the unaffected hemisphere ($U = 14$, $z = -1.54$, $p = 1.12$, $r = -0.39$). Comparisons in patients between pre-Music-supported Therapy and post-Music-supported Therapy evaluation revealed a significant reduction of the AMT in the affected hemisphere ($T = 0$, $p = 0.042$, $r = -0.58$), but no changes were observed in the unaffected hemisphere ($T = 2.25$, $p = 0.207$, $r = -0.36$) in patients. No changes in AMT were observed in controls in both hemispheres ($p > 0.15$ for both comparisons). Any difference was found between groups, time and hemispheres for the CSP. Figure 2 shows the results of RMT, AMT, and CSP.

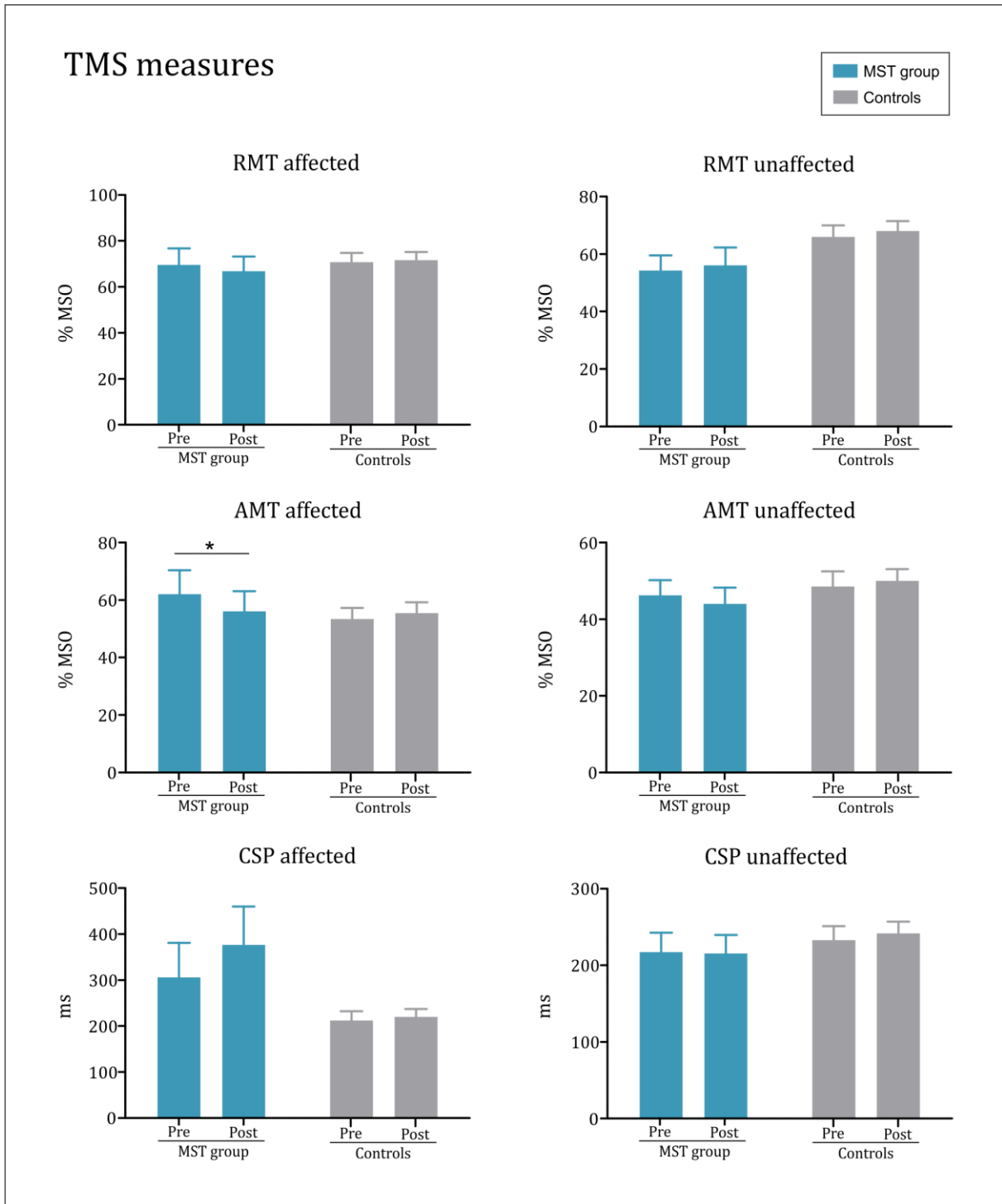


Figure 2. Results of the RMT, AMT, and CSP measures.

For the control group, the hemisphere that is compared to the affected in patients is the one corresponding to their matched participant in the patient's group. The RMT and AMT are expressed in percentages of maximum stimulation intensity (MSO). The CSP is accounted in ms. The AMT of the affected hemisphere decreases in patients after the Music-supported Therapy program ($p = 0.042$). For the RMT and CSP no differences were found in any group ($*p < 0.05$).

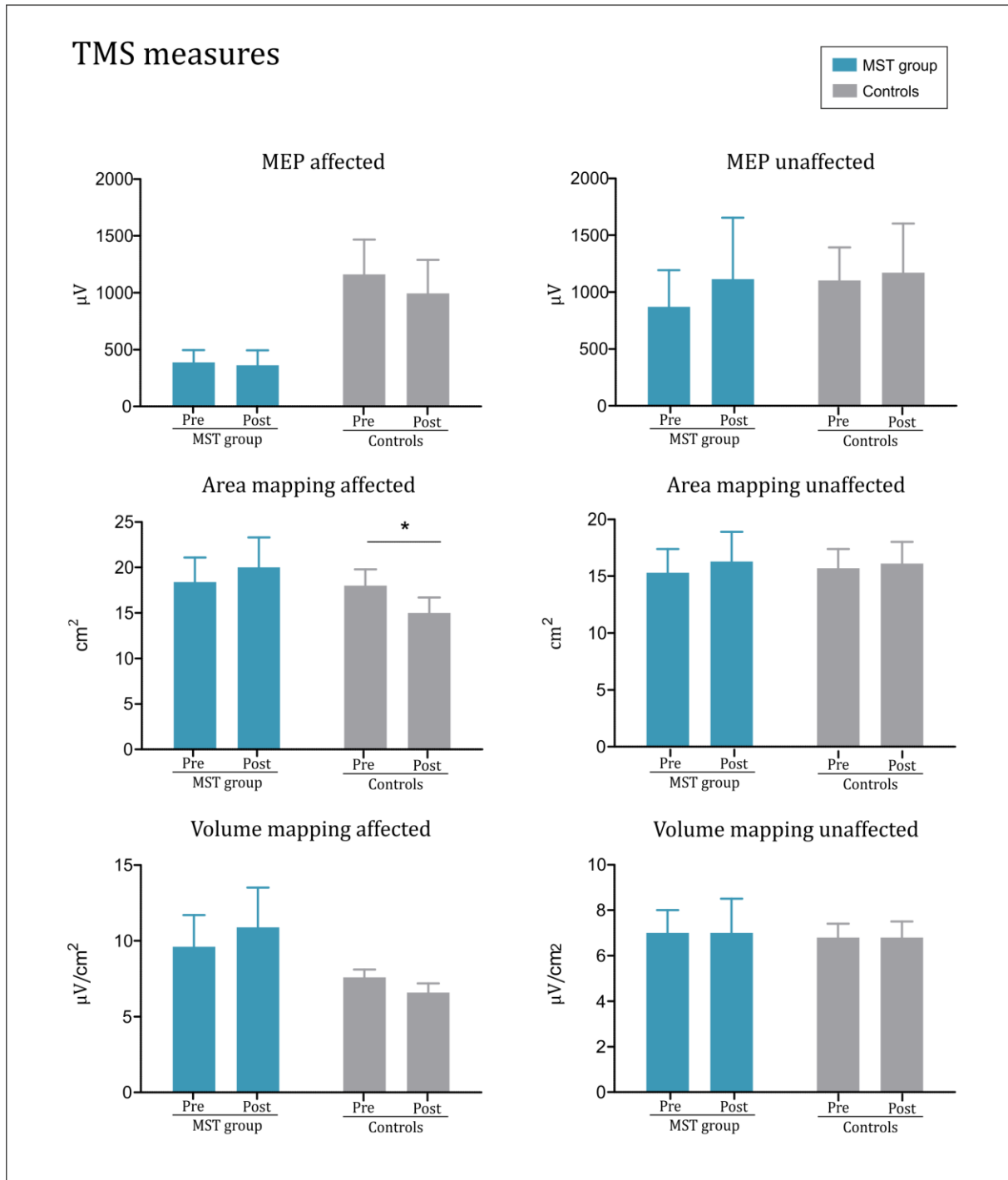


Figure 3. Results of the MEP amplitude and area, and volume of the TMS motor mapping.

For the control group, the hemisphere that is compared to the affected in patients is the one corresponding to their matched participant in the patient's group. The MEP amplitude is expressed in μV , the area in cm^2 and the volume in $\mu\text{V}/\text{cm}^2$. For the MEP amplitude, no differences between groups and across time were encountered. However, control participants seem to show larger amplitude on the elicited MEPs. Regarding to measurements of mapping, no differences were found in the area and volume when comparing groups and across time ($*p < 0.05$).

Regarding the measurements of the motor map, we found a significant between-group difference in the area of the map sustained by a reduction in the post-evaluation in controls ($T = 0, p = 0.018, r = -0.79$). No differences were found for the amplitude of the MEP and volume of the map. Figure 3 shows the results of MEP amplitude, area and volume of the motor map.

However, we found a significant between-group effect in the shift of the CoG_y of the affected hemisphere ($U = 6, z = -2.20, p = 0.028, r = -0.56$) and in the unaffected hemisphere ($U = 7, z = -2.06, p = 0.039, r = 0.55$). Later comparisons only showed a significant posterior shift of the CoG_y of the affected hemisphere in patients ($T = 0, p = 0.043, r = -0.64$) and no changes were observed in the unaffected hemisphere ($T = 1, p = 0.080, r = -0.50$). No changes in CoG_y were observed in controls in both hemispheres ($p > 0.5$ for both comparisons). Figure 4 illustrates the displacement of the motor map in the affected hemisphere and Figure 5 shows the affected motor map of the cortical representation of the FDI muscle of the patients, before and after the therapy.

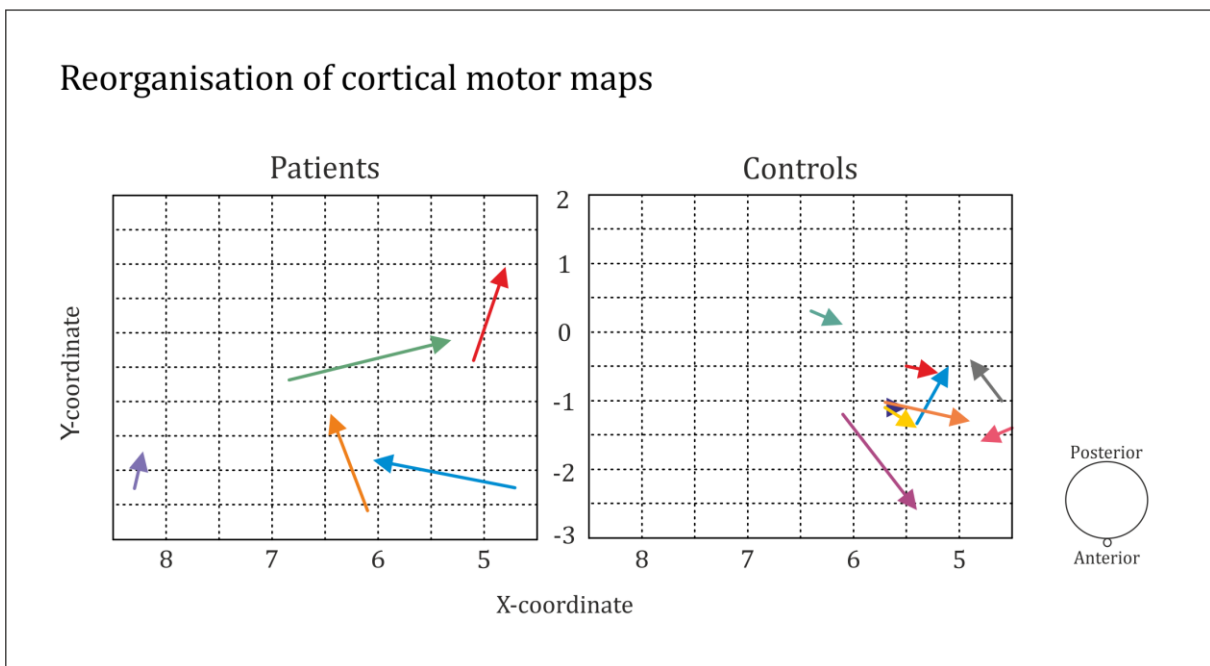


Figure 4. Displacement of the CoG for the cortical maps of the FDI after Music-supported Therapy.

This figure symbolizes the grid where motor maps were drawn and each arrow represents one participant. The beginning of the arrow shows where the CoG (expressed in coordinates x, y) was at baseline and the tip of the arrow indicates the position of the CoG in the post-Music-supported Therapy evaluation. We found a significant shift toward more posterior areas in patients after the Music-supported Therapy program.

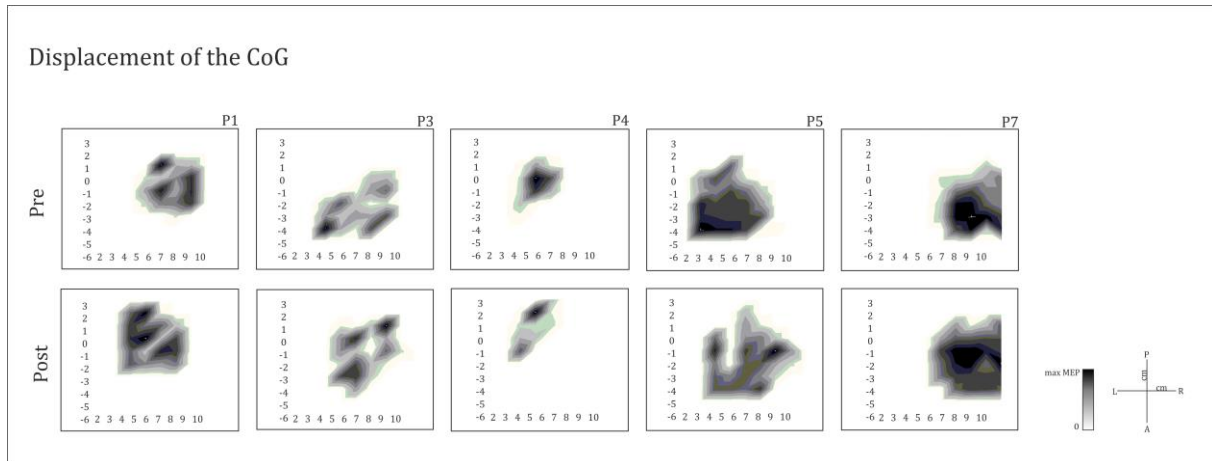


Figure 5. Reorganisation of cortical motor maps.

Cortical motor maps for the first dorsal interosseus (FDI) muscle of the affected hand before and after Music-supported Therapy for 5 patients (P1, P3, P4, P5, and P7). Values are normalized for each patient according to their maximum MEP amplitude (μV). Moreover, we added units in the part of the manuscript describing the TMS protocol and we improved the definition of each parameter of TMS.

3.4 Discussion

Music-supported Therapy program improved motor function and quality of life of nine stroke patients accompanied by changes in the organisation of the sensorimotor cortex, evidenced by a decreased AMT and a displacement of the motor map (CoG_y).

Reduction of motor deficits was reflected by improvements in the ARAT, APS and BBT test. These results are in congruence with previous studies validating the application of Music-supported Therapy in stroke patients (Altenmüller et al., 2009; Amengual et al., 2013; Rojo et al., 2011; Schneider et al., 2007). As motor function was evaluated using motor test independent of and different from the music performance trained in the Music-supported Therapy, this argues clearly for generalisation of the effects of Music-supported Therapy to everyday movements. This is critical for a more widespread clinical application.

When playing the piano, patients have to perform fine movements with the affected hand to press the key in order to elicit the tone (Zatorre et al., 2007). This sensory feedback is thought to be essential in the success of the therapy (Rodriguez-Fornells et al., 2012) as patients have to readjust their movements in terms of temporal and spatial organisation, coordination according to the rhythm, force and velocity. This idea is also in agreement with the essential role of audio-motor interactions in music processing (Zatorre et al., 2007) and the potential increase of plasticity when using multimodal learning paradigms (Herholz & Zatorre, 2012; Lappe, Herholz, Trainor, & Pantev, 2008; Pantev & Herholz, 2011; Wan & Schlaug, 2010). Furthermore, working with scales, tones and melodies allows a wide range of different sequences giving the task a

greater variability. Such task variations enhance the creation of internal models which might be crucial to generalise motor skill learning to other different situations (Conditt et al., 1997).

While the improvement on motor tests seen here suggests a generalisation to movements important for everyday tasks this conclusion needs to be substantiated. Gains in hand function in terms of greater strength and dexterity contribute to improvements in the functional use of the hand (Harris & Eng, 2007; Wolf et al., 2008) which in turn diminishes the level of disability and improves social participation (Carod-Artal et al., 2000; Wolf et al., 2008). However, improvements in motor function can take several months to become apparent in activities of daily living (Winstein et al., 2004). When validating new neurorehabilitation techniques, it is crucial not only to test their efficacy, known as the degree to which the intervention affects functional outcome measures but also to assess their effectiveness and how the therapy is influencing the quality of life (Nadeau, 2002). At this time, we only have results from the Stroke-specific Quality of Life Scale where patients reported better quality of life. Future studies should include a follow-up evaluation and a comprehensive assessment of basic and instrumental activities of daily life, taking into account information from patients and caregivers.

Regarding the motor threshold, AMT was decreased after the therapy showing a change in excitability of motor cortex. It has been postulated that motor thresholds could decrease during motor skill learning although this could be reestablished when the skill becomes overlearned (Pascual-Leone et al., 1995; Pearce, Thickbroom, Byrnes, & Mastaglia, 2000). An inter-hemispheric asymmetry in motor thresholds has been described after unilateral damage to the corticomotor pathways (Groppa et al., 2012). In stroke, motor thresholds are increased in the affected hemisphere suggesting that cortical neurons increase their thresholds for excitation (McConnell et al., 2001; Traversa, Cicinelli, Pasqualetti, Filippi, & Rossini, 1998). RMT, measured at rest, depends on the excitability of presynaptic neurons to the corticospinal tract, the excitability of synapses at the cortex between excitatory inputs and corticospinal cells and the synaptic strength between the pyramidal neurons of the corticospinal tract and the motoneurons in the spinal cord (Talelli, Greenwood, & Rothwell, 2006). Differently, AMT, measured when the muscle is contracted voluntarily by the subject, mainly depends on the membrane excitability, since synapses are pre-activated due to the contraction of the muscle. Therefore, changes in AMT might explain specific regulation of the excitability at a cortical level rather than spinal. A reduction in AMT, therefore, might signal functional recovery, as less intense stimulus-pulses elicit MEPs during tonic voluntary activity (Kobayashi & Pascual-Leone, 2003).

Differences in CoG_y showed changes of the motor map in terms of a posterior displacement in the vertical axis of the map. Functional motor recovery correlates with the reorganisation of pyramidal neurons in the somatosensory cortex of the affected hemisphere (Pekna et al., 2012). Cortical motor output zones can expand to adjacent areas (Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001; Nudo & Milliken, 1996) and this displacement is associated with successful motor recovery (Jaillard et al., 2005). The posterior displacement of activation we encountered suggests a reorganisation of the motor representations. In their study validating the Music-supported Therapy in a group of chronic patients, Amengual and colleagues (2013) reported a shift in CoG_x, the coordinate of the CoG that represents the horizontal axis of the map, which demonstrates cortical reorganisation after the Music-supported Therapy program (Amengual et al., 2013). Similar findings, albeit outside of the context of Music-supported Therapy, have been reported by Pineiro and colleagues (2001) and Calautti and colleagues (2003) (Calautti, Leroy, Guincestre, & Baron, 2003; Pineiro, Pendlebury, Johansen-Berg, & Matthews, 2001). It has been seen that repetitive motor training, which is based on the repetition of an active motor sequence, does not produce functional reorganisation of cortical maps (Jaillard et al., 2005). However, motor skill acquisition, the process by which movements are executed more quickly and accurately with practice to accomplish a functional objective, leads to changes in the representation of a muscle in the motor cortex (Nudo, 2006; Willingham, 2001). This, in turn, suggests that the characteristics of Music-supported Therapy are especially suited to induce motor plasticity.

Previous studies evaluating the size of the motor maps after training in healthy participants (Pascual-Leone, Grafman, & Hallett, 1994; Pascual-Leone et al., 1995) and in stroke patients (Liepert et al., 2000; Liepert et al., 1998) described an increase in the number of cortical sites responding to a target muscle (Pekna et al., 2012). We did neither find changes in the area and volume of motor maps nor on the CSP and MEP amplitude measures after Music-supported Therapy. One reason for this lack of findings in the area and volume of motor maps from patients might be the small sample size used. Future studies should, therefore, include more patients to confirm the Music-supported Therapy effects on the reorganisation of the sensorimotor cortex. Such larger scale studies should also differentiate between patients with cortical and subcortical lesions and lesions of the dominant versus non-dominant hemisphere. Neuroimaging techniques, especially fMRI and brain connectivity analysis should also be included in complementing this information. Moreover, an important limitation of the study is the lack of a control group of patients. In the present study, only a healthy control group was evaluated to reject the idea that changes in the excitability of the sensorimotor cortex are due to systematic time-dependent effects or possible brain changes over time (Johansen-Berg, 2012). Contrary to the expectations, we found that the area of the motor map was reduced in healthy participants. We could not

clarify this point as we did not control if those participants did any type of motor learning during the pre and post evaluation that would explain changes in the area of the motor map (Pascual-Leone et al., 1994). For that reason, this effect limits the conclusions of the present study. Other studies have shown the benefits of Music-supported Therapy comparing two groups of patients with different interventions, Music-supported Therapy and conventional treatment (Altenmüller et al., 2009; Schneider et al., 2007). These designs are more appropriate and will be necessary for future studies when evaluating the effects of Music-supported Therapy on the brain plasticity in stroke patients.

Finally, it is worth mentioning that music always entails emotion. Its emotional value might be important for the acceptance of the therapy program and its efficacy (Schneider et al., 2010). It has been suggested that neuroplasticity depends on the motivational value of the activity (Sanes & Donoghue, 2000). Therefore, the creation and validation of new therapies and their application into clinical practice should take emotional and motivational factors into account with the introduction of meaningful activities in the neurorehabilitation process.

Study 2

Chapter 4. Study 2

Music-supported Therapy in the rehabilitation of subacute stroke patients: a Randomised Controlled Trial¹

4.1 Introduction

Stroke is one of the main causes of death and long-term disability and is a significant burden on individuals and healthcare systems (Feigin et al., 2015; Murray et al., 2012). Among other consequences, the majority of stroke survivors present paresis of the upper extremity (Rathore et al., 2002). These deficits can lead to limitations in activities of daily life and restrictions in participation, thus decreasing the quality of life (QoL) of stroke patients (Mayo et al., 2014, 2002).

The recovery of motor deficits relies on rehabilitation programs, which are based on the principles of individualisation, high intensity, and mass repetition of movements (Albert & Kesselring, 2012). These programs usually include physiotherapy and occupational therapy sessions on a daily basis during the first 6 months and up to a year following the stroke (Langhorne et al., 2011). In these sessions, a wide range of techniques are used, although a recent meta-analysis only supported the use of modified constraint-induced movement therapy and task-specific training in the first four weeks poststroke (Wattchow, McDonnell, & Hillier, 2018). In addition, other emerging evidence-based techniques could be introduced into the rehabilitation programs as add-on treatments to boost the recovery of stroke patients (François, Grau-Sánchez, Duarte, & Rodríguez-Fornells, 2015; Hatem et al., 2016). These techniques are designed to improve not only motor deficits but also other relevant aspects, including motivation, treatment adherence, and mood, all of which are known to contribute to the success of the rehabilitation process (Luker, Lynch, Bernhardsson, Bennett, & Bernhardt, 2015; Poltawski et al., 2015). For instance, music practice as a therapy for stroke patients is an enjoyable activity that includes complex and coordinated movements while placing a high

¹ The results presented in this chapter correspond to:

Grau-Sánchez, J., Duarte, E., Ramos-Escobar, N., Sierpowska, J., Rueda, N., Redón, S., ... & Rodríguez-Fornells, A. (2018). Music-supported therapy in the rehabilitation of subacute stroke patients: a randomized controlled trial. *Annals of the New York Academy of Sciences*. In press. doi: 10.1111/nyas.13590

demand on cognitive functions, such as attention and working memory, as well as modulating mood (Alves-Pinto, Turova, Blumenstein, & Lampe, 2016; Lampe et al., 2015; Raghavan et al., 2016; Raglio et al., 2017; Sihvonen et al., 2017). Music performance facilitates auditory-motor coupling (Ripollés et al., 2016), increases the adherence to physical exercises (Wininger & Pargman, 2003) and promotes social bonding during group performance (Cirelli, Einarson, & Trainor, 2014; Guerrero, Turry, Geller, & Raghavan, 2014; Hove & Risen, 2009). Some of these positive aspects could be partly mediated by the dopaminergic reward system, which is known to be highly responsive to music and involved in learning, memory, and the modulation of synaptic plasticity (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Lisman et al., 2005). Recently, optimisation of motor learning has also been closely associated with intrinsic motivational factors (Wulf & Lewthwaite, 2016). Both intensive motor training and motivational aspects could be effectively combined during music practice to improve motor recovery.

Specifically, Music-supported Therapy (Schneider et al., 2007) aims to enhance the motor deficits of the upper extremity through the training with musical instruments and provides real-time auditory feedback about the performance, which serves as a basis for motor learning (Rodriguez-Fornells et al., 2012; Zatorre et al., 2007). Studies in the subacute and chronic stage of the rehabilitation process have demonstrated that stroke patients boost their motor function after the Music-supported Therapy training (Altenmüller et al., 2009; Rojo et al., 2011; Schneider et al., 2007; Tong et al., 2015). A four-week program of Music-supported Therapy can improve dexterity, smoothness, and velocity of movements and induce intrahemispheric functional reorganisation within the lesioned hemisphere (Amengual et al., 2013; Grau-Sánchez et al., 2013; Ripollés et al., 2016). Music-supported Therapy targets motor deficits, but it can boost some aspects of cognition, mood, and QoL (Ripollés et al., 2016). Although the use of music-based therapies for the neurological population seems promising, high-quality randomised controlled trials (RCTs) are scarce (Magee et al., 2017). Moreover, it is still unclear whether adding Music-supported Therapy to the conventional rehabilitation program can enhance motor recovery in subacute stroke patients. Furthermore, no previous study has directly compared the changes observed in emotional and QoL domains of subacute stroke patients treated with Music-supported Therapy to standard treatment.

In this study, an RCT was designed with the aim of testing the effectiveness of adding Music-supported Therapy to a program of conventional rehabilitation for subacute stroke patients. In contrast to previous studies with similar aims (Schneider et al., 2007), in the present RCT, we controlled for the duration of the intervention provided to participants, making it equal in the experimental and the control groups. We hypothesised that patients treated with additional

Music-supported Therapy would show a major improvement in their upper extremity motor function compared with patients treated only with conventional therapies. We also expected an enhancement in other cognitive domains as well as in mood and QoL after receiving Music-supported Therapy. Finally, and considering the importance of intrinsic motivation and engagement in the treatment success (Wulf & Lewthwaite, 2016), we predicted that motor improvements in the MST-group would be related to patient's individual differences in their capacity to experience pleasure in music activities.

4.2 Methodology

4.2.1 Study design

A two-arm, parallel-group RCT was conducted in which a program of four weeks of Music-supported Therapy was compared with conventional therapy in addition to a standard rehabilitation program. Before and after the four-week treatment, the motor and cognitive functions as well as mood and QoL of the participants were evaluated. A follow-up evaluation of motor functions was also carried out at 3 months to assess the retention of gains. The study was approved by the ethical review board of the Hospital del Mar Medical Research Institute in Barcelona (registered trial at clinicaltrials.gov, ID:NCT02208219).

4.2.2 Participants

Subacute stroke patients involved in a program of outpatient rehabilitation at the Department of Physical Medicine and Rehabilitation at the Hospitals del Mar i de l'Esperança were assessed for recruitment from December 2013 to May 2017. Eligibility criteria were: (i) mild-to-moderate paresis of the upper extremity after a first-ever stroke, (ii) less than 6 months after the stroke, (iii) age between 30 and 75 years, (iv) no major cognitive deficits affecting comprehension (Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) > 24), (v) no neurological or psychiatric co-morbidity, (vi) no previous formal musical education, and (vii) ability to speak Spanish and/or Catalan. Mild-to-moderate paresis was defined as having a score between 2 and 4 in the Medical Research Council Scale for Muscle Strength (Medical Research Council, 1976) at the distal muscles of the upper extremity.

The recruitment was performed by a medical doctor specialised in physical medicine and rehabilitation who provided information about the study in written and verbal format. Patients who agreed to participate signed an informed consent form.

4.2.3 Randomisation

Participants were randomly allocated to a group receiving Music-supported Therapy (MST-group, n=20) or to a conventional therapy group (CT-group, n=20) in addition to the standard program of rehabilitation. The randomisation was stratified for laterality of the affected extremity. A statistician prepared a computer-generated random sequence, which was only accessible to one member of the research team who did not take part in the enrollment, evaluation, or treatment sessions. This researcher was responsible for informing the therapist about the group allocation of the participant at the beginning of the intervention.

4.2.4 Treatment

Both groups received an outpatient rehabilitation program that consisted of two 1-hour group sessions of occupational therapy and physiotherapy a day (5 days per week, 10 hours in total per week). During the occupational therapy sessions, functional and task-specific activities were trained to improve the motor performance of the affected upper extremity. In the physiotherapy sessions, patients exercised walking, balance, and global mobility. In addition to this standard program, participants were randomised into the MST or CT-group to receive 20 individual sessions (5 sessions per week, 30 min each) of Music-supported Therapy in the MST-group or extra time of exercises for the upper extremity in the CT-group.

Participants in the MST-group were trained to play a keyboard and an electronic drum set with the affected upper extremity following a modular therapy regime with a stepwise increase of complexity. Participants in the CT-group received individual training of the upper extremity, which included passive mobilisation, stretch and progressive resistance exercises, and task-specific training. This group was conceived as an active control group (see Appendix for a detailed explanation of exercises in the MST and CT-groups). In both groups, the number of additional training hours was equal, and the sessions were administered individually by an occupational therapist.

4.2.5 Evaluation of participants

Demographic and clinical variables, such as age, gender, etiology of stroke, lesion location, date of stroke, and the scores of the National Institutes of Health Stroke Scale (Brott et al., 1989) and the modified Rankin Scale (Van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988) at discharge of the stroke unit, were collected from medical records.

Primary outcome. The primary outcome was the functional movements of the paretic upper extremity measured with the Action Research Arm Test (ARAT, Lyle, 1981) at the end of the treatment.

Secondary outcomes

Motor outcomes. Two measures of motor impairment were used: the upper extremity subtest of the Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA, Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975) and grip strength (Mathiowetz, Weber, Volland, Kashman, & Cummings, 1984) measured with a dynamometer as the mean of three trials. Fine dexterity was assessed with the Nine Hole Pegboard Test (9HPT, Parker et al., 1986) and Box and Blocks Test (BBT, Mathiowetz et al., 1985). The functional use of the affected extremity in activities of daily living was evaluated with the Chedoke Arm and Hand Activity Inventory (CAHAI, Barreca et al., 2015). The motor function evaluation was performed at baseline, after the intervention, and at a 3-month follow-up by an occupational therapist with experience in neurorehabilitation.

Cognitive outcomes. The cognitive evaluation was specifically focused on executive functions and memory. Working memory and attention were evaluated using the digit span (forward and backward) subtest from the Wechsler Adult Intelligence Scale III (Wechsler, 1944), response inhibition by the Stroop task (Stroop, 1992), and processing speed and mental flexibility by the Trail Making Test (Reitan, 1958). Furthermore, the Rey Auditory Verbal Learning Test (RAVLT, Rey, 1964) and the story recall from the Rivermead Behavioral Memory Test (Wilson et al., 2008) were both used to assess verbal memory. The cognitive assessment was performed at baseline and after the intervention by a neuropsychologist.

Mood and QoL outcomes. Mood was evaluated with the Profile of Mood States (McNair, Lorr, & Droppleman, 1971), the Beck Depression Inventory Scale (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988), and the Apathy Evaluation Scale (Marin et al., 1991). QoL was assessed with the Stroke-specific Quality of Life Scale (Williams et al., 1999) and health-related QoL with the Health survey questionnaire SF-36 (Alonso, Prieto, & Antó, 1995). Questionnaires for mood and QoL were given to patients to be filled out at home before and after the treatment. The Barcelona Music Reward Questionnaire (Mas-Herrero, Marco-Pallares, Lorenzo-Seva, Zatorre, & Rodriguez-Fornells, 2013) was completed by patients at baseline to evaluate individual differences in their capacity to experience pleasure from engaging in musical activities.

4.2.6 Blinding

All of the evaluators were blinded to participants' assigned treatment groups. Participants were inevitably aware of the treatment received, but they were asked not to inform the evaluators about the intervention, and no information about the specific differences between groups was provided to them.

4.2.7 Statistical analysis

Statistical analysis was performed using SPSS 21 software (SPSS Inc, Chicago, IL, USA). A *t*-test for independent samples and the Pearson χ^2 test were used for quantitative and nominal variables to test differences between groups at baseline. To test the effect of the intervention between groups, *t*-tests for independent samples were used for the change scores from baseline to posttreatment and from baseline to follow-up at 3 months. The within-group differences were tested using paired samples *t*-tests. The level of significance was set at 0.05.

4.3 Results

4.3.1 Demographic and clinical characteristics

A total of 178 stroke patients receiving an outpatient rehabilitation program at the recruitment site were assessed for eligibility (Figure 1). Among them, 129 did not meet the inclusion criteria, and 9 declined to participate. Of the 40 patients enrolled in the study, 20 were assigned to the MST-group and 20 to the CT-group. In the MST-group, one patient was transferred to another clinic after randomisation. There were no significant differences in demographic and clinical variables between groups at baseline, as outlined in Table 1, except for the variable aetiology of stroke and number of participants with cortical lesions. The CT-group had a major distribution of hemorrhagic strokes compared with the MST-group, and the number of participants who had lesions that involved cortical regions was higher in the MST-group than in the CT-group (for a detailed clinical description of participants, see Table 2). The number of hours of rehabilitation that patients received before enrollment was equal between groups. Importantly, there were no significant differences between groups at baseline in any of the assessments used for primary and secondary outcomes.

At the follow-up evaluation at 3 months, three participants in the MST-group (two unable to contact and one withdraw) and two participants (unable to contact) in the CT-group dropped out. With regard to the secondary outcomes, some participants could not complete all the

questionnaires at the post-treatment evaluation owing to fatigue but were included in the study, as they underwent most of the evaluation. The exact number of participants per test is provided in Tables 3, 4, 5 and 6.

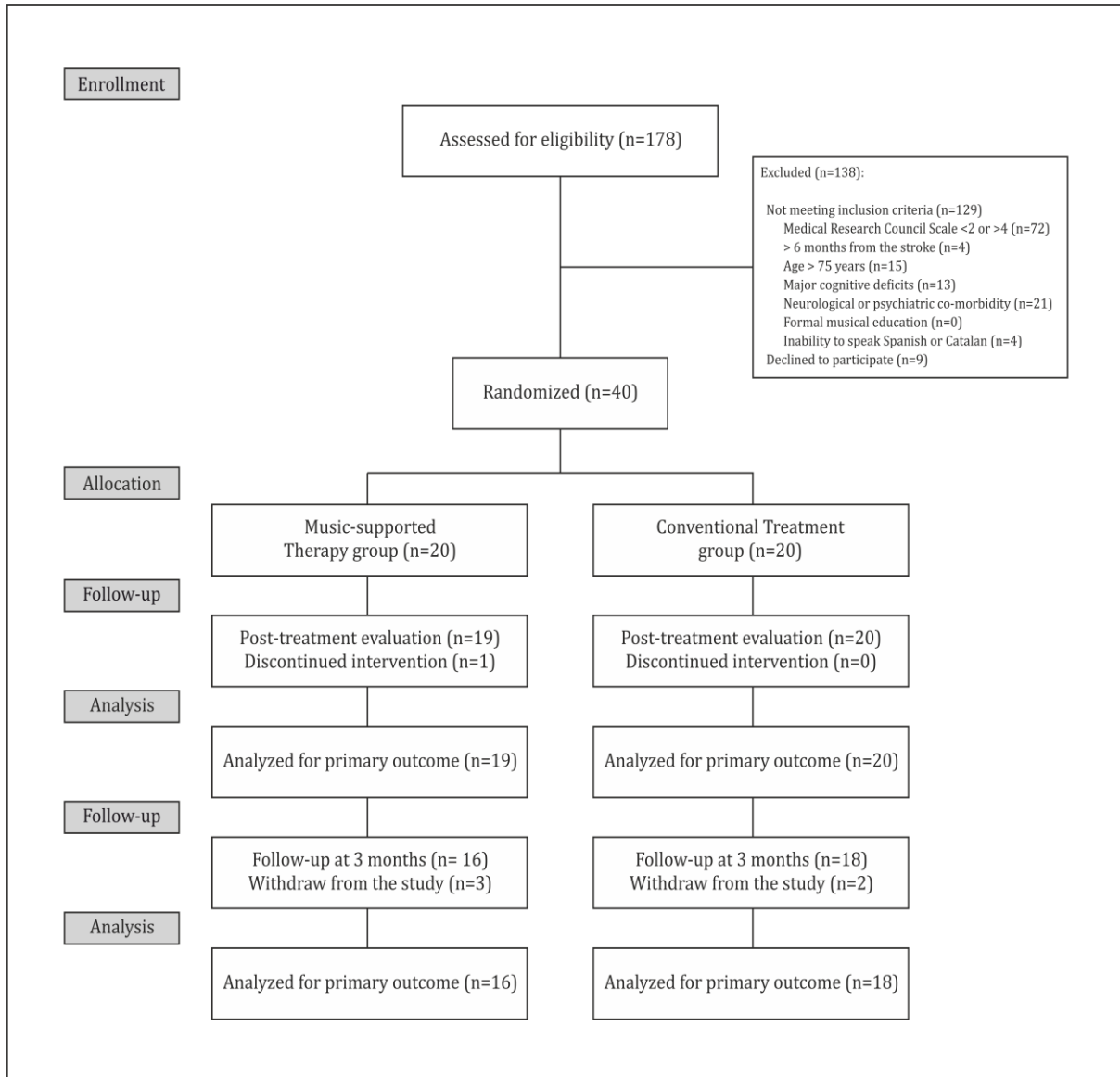


Figure 1. Study design and participant flow.

Flow diagram with the phases of the two-arm, parallel randomized controlled trial and the number of participants per group in each of the phases.

Table 1. Demographic and clinical variables for both groups at baseline.

	MST group (n=19)	CT group (n=20)	p-value
Demographic variables			
Age (range)	60.1 (45-74)	62.5 (49-72)	.314
Gender			
<i>Females (%)</i>	8 (42.1)	8 (40)	.894
<i>Males (%)</i>	11 (57.9)	12 (60)	
Clinical variables			
Stroke etiology			
<i>Ischaemic (%)</i>	18 (94.7)	14 (70)	.044*
<i>Haemorrhagic (%)</i>	1 (5.3)	6 (30)	
Lesion location			
<i>Cortical (%)</i>	7 (36.8)	1 (5)	.014*
<i>Subcortical (%)</i>	16 (84.2)	16 (80)	.732
<i>Brainstem (%)</i>	2 (10.5)	3 (15)	.676
<i>Cerebellum (%)</i>	1 (5.3)	0 (0)	.299
Time since stroke (range)	65.8 (32-162)	64.9 (28-136)	.085
NIHSS* (range)	5.8 (2-14)	5.3 (2-9)	.434
Modified Rankin Scale (range)	3.5 (3-4)	3.2 (2-4)	.237
FMA* baseline (range)	45.3 (24-65)	45.8 (21-65)	.904
Rehabilitation received before enrollment			
Physiotherapy	26.6 (20.4)	17 (12.1)	.088
Occupational Therapy	23.5 (19.7)	19.1 (16)	.452
Speech therapy	14.2 (12.4)	12.2 (5.9)	.784
Reward in musical activities			
Barcelona Music Reward Questionnaire	73.9 (10.6)	71.8 (13.6)	.594

Absolute frequencies are shown for the variables gender, stroke etiology and lesion location. For the rest of variables the mean and standard deviation are shown except indicated otherwise. The differences between groups were evaluated with *t*-test for independent samples for quantitative variables and the Pearson χ^2 test for nominal ones. *NIHSS, National Institutes of Health Stroke Scale; FMA, Fugl-Meyer Assessment of Motor Recovery after Stroke; $p < 0.05$.

Music-supported Therapy group (MST-group)

Age	Gender*	Etiology*	Laterality *	Lesion location	Lesion size	NIHSS*	mRS*	Time since stroke	Level of motor impairment
52	F	I	L	Insula, postcentral gyrus, inferior parietal lobe, caudate and lenticular nuclei, internal capsule, and corona radiata.	34352	14	4	162	25
60	F	I	L	Precentral and postcentral gyrus.	9034	5	3	39	24
73	M	I	R	Pons.	569	5	4	82	33
45	F	I	L	Caudate and lenticular nuclei, and internal capsule.	4470	5	4	39	65
58	M	I	R	Middle and inferior frontal gyrus, precentral and postcentral gyrus and insula.	44081	3	3	46	62
63	F	I	L	Dorsolateral prefrontal cortex, semioval center, frontal lobe and insule.	-	7	4	67	43
61	M	I	R	Insula, frontal and parietal lobes.	139987	5	3	61	45
58	M	I	R	Internal capsule.	-	5	3	54	54
64	F	I	L	Frontal, parietal, temporal and occipital lobes.	16580	8	4	121	29
60	M	I	R	Pons.	890	8	4	76	41
55	M	I	L	Corona radiate.	1827	4	3	33	65
56	M	I	L	Lenticular nucleus and internal capsule.	4873	6	3	55	29
59	M	I	L	Internal capsule.	6857	5	3	32	63
46	F	I	R	Frontal and parietal lobes, globus pallidus and internal capsule.	10083	2	3	34	58
66	M	I	L	Insula, lenticular nucleus and internal capsule.	-	8	3	41	46
57	M	I	L	Cerebellar hemisphere.	38266	4	3	50	57
62	F	I	R	Caudate and lenticular nuclei, and internal capsule.	10650	3	4	49	35
74	M	I	L	Internal capsule.	155	6	4	155	45
73	F	H	R	Internal capsule and thalamus.	5745	9	4	56	43

Conventional Therapy group (CT-group)										
Age	Gender*	Etiology*	Laterality*	Lesion location	Lesion size	NIHSS*	mRS*	Time since stroke	Level of motor impairment	
52	F	H	R	Lenticular nucleus, internal capsule and thalamus.	2428	6	4	97	55	
69	F	I	R	Caudate and lenticular nuclei, and internal capsule.	2388	6	4	63	41	
52	M	I	L	Internal capsule and thalamus.	1328	3	3	49	50	
63	F	I	R	Frontal and temporal lobes, insula.	44398	8	3	60	57	
65	M	I	R	Pons.	753	7	4	80	21	
56	M	I	L	Corona radiate.	297	5	4	39	46	
65	M	I	L	Caudate and lenticular nuclei.	3218	5	3	135	39	
49	M	I	L	Pons.	821	4	2	34	43	
56	M	H	L	Frontal lobe.	24085	2	3	28	65	
72	M	H	L	Frontal, parietal and occipital lobes.	36375	6	4	53	54	
63	F	I	L	Lenticular nucleus, internal capsule and thalamus.	2228	6	3	59	30	
62	F	I	R	Parietal, and occipital lobes.	-	6	3	49	54	
59	M	I	R	Anterior cingulate gyrus.	1983	3	2	36	47	
70	F	I	R	Internal capsule.	5332	5	3	60	53	
70	M	I	L	Semioval center and caudate and lenticular nuclei.	1720	5	4	136	38	
60	F	H	R	Caudate and lenticular nuclei, internal capsule, and corona radiata.	49245	5	3	52	49	
68	F	H	R	Internal capsule and thalamus.	-	6	3	80	30	
67	M	I	R	Frontal and parietal lobes, caudate and lenticular nuclei and corona radiata.	6525	4	3	41	55	
66	M	I	L	Pons.	1767	8	3	63	51	
66	M	H	L	Lenticular nucleus, internal capsule and thalamus.	2572	9	4	85	39	

Table 2. Clinical description of participants.

*F, female; M, males; H, haemorrhagic; I, ischaemic; R, right; L, left; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. Lesion size is expressed in mm³, time since stroke is in days and the level of motor impairment is the Fugl-Meyer Assessment of Motor Recovery after Stroke score at baseline.

4.3.2 Primary outcome

For the overall score of the ARAT, no differences in change scores were found between groups at post-treatment and 3-month follow-up (Figure 2 and Table 3). Both groups significantly improved after the intervention. The MST-group had a mean improvement of 9.8 (± 7.9) points after the treatment ($t(18) = -5.37, p = 0.001, d = 1.23$) and 12.4 (± 14) at the follow-up evaluation ($t(15) = -3.55, p = 0.003, d = 0.89$). The CT-group improved 6.7 (± 7.9) points after treatment ($t(19) = -3.75, p = 0.001, d = 0.84$) and 7.3 (± 8.1) at the follow-up performed at 3 months ($t(17) = -3.82, p = 0.001, d = 0.90$). The Minimal Detectable Change (MDC) for this test is a score of 5.7 points and 14 of 19 participants in the MST-group reached the MDC level after treatment and 11 out of 16 did it at 3 months. In the CT-group, 9 of 20 participants presented a change that was clinically relevant after treatment and 9 out of 18 reached the MDC level at 3 months (Fig. 2). The difference between groups in the number of patients that reached the MDC was not significant ($\chi^2(1) = 3.31, p = 0.069$ for post-treatment and $\chi^2(1) = 1.22, p = 0.268$ for follow-up).

4.3.3 Secondary outcomes

Regarding the secondary motor outcomes, no significant differences were observed for the group comparisons after treatment or at follow-up (Figure 2 and Table 3). The within-group analyses revealed that both groups improved after treatment and at follow-up in the FMA, 9HPT, BBT and the CAHAI (Table 3).

Table 3. Results for the primary and secondary motor outcomes.

Motor test	MST-group			CT-group			MST-group		CT-group		Between groups Baseline Post-test	Between groups Baseline Follow-up
	Baseline	Post-test	<i>p</i>	Baseline	Post-test	<i>p</i>	Follow-up	<i>p</i>	Follow-up	<i>p</i>		
Primary outcome												
Action Research Arm Test	34.6 (16.3)	44.4 (16.1)	.001	39.9 (12)	46.5 (11.6)	.001	50 (13.9)	.003	47.9 (11.3)	.001	.225	.191
<i>Grasp</i>	11.2 (5.8)	14.1 (5.3)	.003	12.6 (3.5)	14.5 (3.8)	.002	15.8 (4.3)	.009	15.1 (3.6)	.001	.313	.283
<i>Grip</i>	7.6 (2.8)	9.9 (3.2)	.001	8.6 (2.5)	10.3 (2.1)	.002	10.6 (3.1)	.001	10.5 (2.2)	.004	.325	.501
<i>Pinch</i>	9.2 (6.4)	12.8 (6.4)	.001	11.6 (4.8)	13.9 (4.7)	.005	15.7 (4.6)	.003	14.6 (4.1)	.013	.228	.124
<i>Gross Movement</i>	6.6 (2.7)	7.6 (1.8)	.004	7.1 (2.4)	7.9 (1.8)	.078	8 (2.2)	.078	7.8 (2)	.012	.696	.538
Secondary Motor outcomes												
Fugl-Meyer Assessment of Motor Recovery after Stroke	45.3 (13.7)	53.7 (11.4)	.001	46.6 (10.3)	54.7 (9.9)	.001	57.1 (10.7)	.001	57 (8.3)	.001	.914	.722
Grip strength	12.8 (9.4)	14.7 (11.6)	.111	11.3 (8.8)	12.5 (9.5)	.213	18.9 (12.7)	.038	13.1 (7.9)	.323	.648	.240
Nine Hole Pegboard Test	66.5 (29.6)	41.5 (18.1)	.001	57 (34.8)	39.8 (26.6)	.017	34.6 (10.3)	.001	31.3 (14.3)	.006	.368	.368
Box and Blocks Test	24.6 (15.9)	33.7 (15.5)	.001	30.5 (15.7)	37.5 (15.4)	.015	43.3 (14.3)	.001	40.9 (15.9)	.008	.545	.216
Chedoke Arm and Hand Activity Inventory	52.9 (24.7)	72.1 (19.7)	.001	59.2 (17.2)	75.5 (12.8)	.001	80.2 (17.8)	.001	77.2 (15.9)	.001	.486	.215

The mean scores and standard deviations are shown for the primary and secondary motor outcomes for both the MST and CT-groups at baseline, post-treatment (post-test) and follow-up at 3 months. The dependent *t*-test for paired samples was used to test within-groups comparisons between baseline and post-test scores, and baseline and follow-up scores. The between-groups comparisons were analysed using independent *t*-tests with the change scores from baseline to post-test and baseline to follow-up. The scores obtained by groups are presented for each test except for the grip strength, which is expressed in Kg, and the Nine Hole Pegboard Test, expressed in seconds. Some participants could not complete the Nine Hole Pegboard Test (MST-group n=15 at baseline and post-test; CT-group n=16 at baseline and post-test and n=15 at follow-up), the Fugl-Meyer Assessment of Motor Recovery after Stroke and grip strength (CT-group n=19 at baseline and post-test).

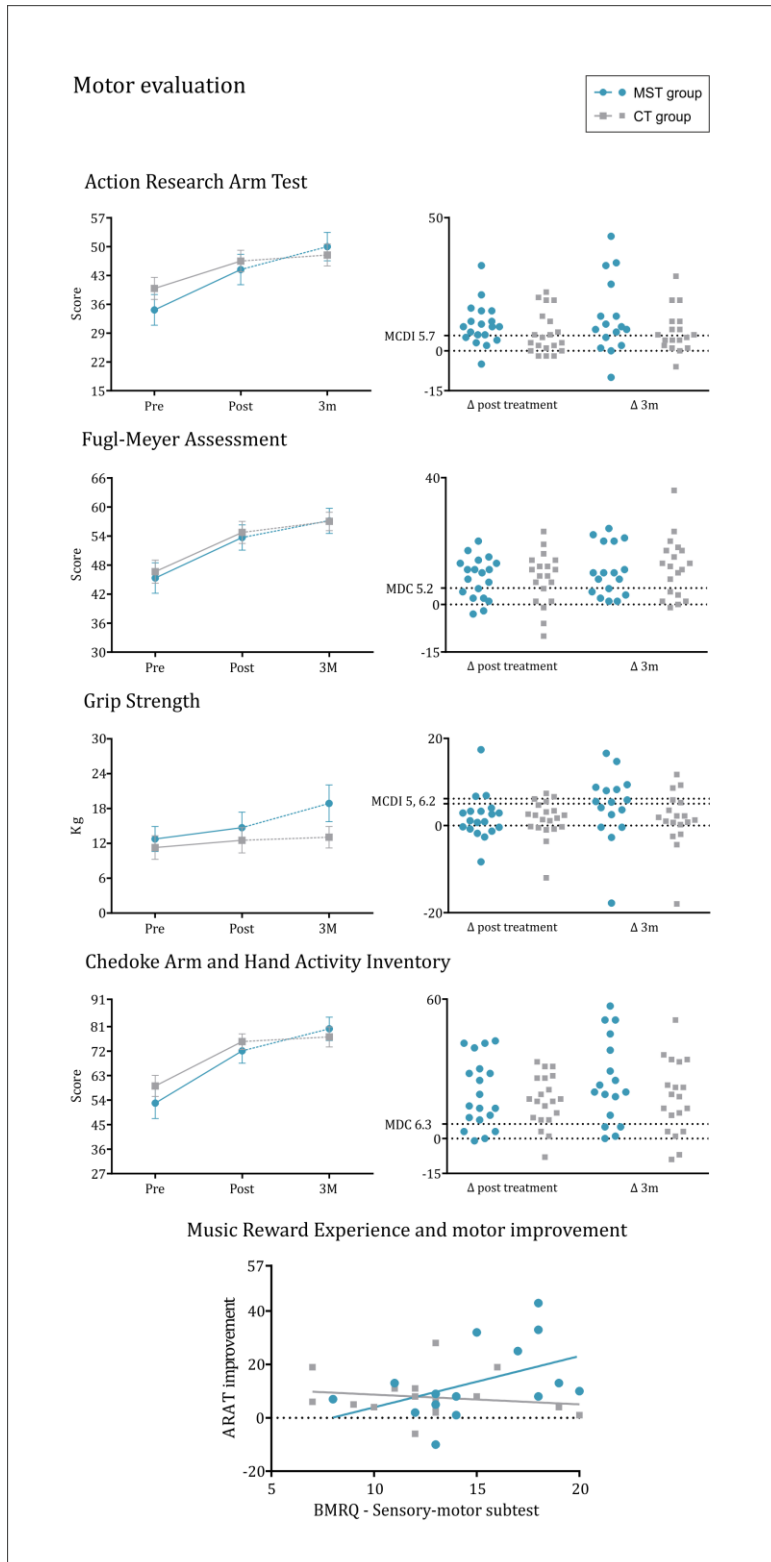


Figure 2. Results for the primary and secondary motor outcomes.

Results for the Action Research Arm Test (ARAT), the Fugl-Meyer Assessment of Motor Recovery after Stroke, the grip strength, and the Chedoke Arm and Hand Activity Inventory at baseline (pre), after the intervention (post) and at the 3 months followup (3 months) are shown for both groups. For each test, the improvements from baseline to posttreatment (Δ posttreatment) and from baseline to the follow-up at 3 months (Δ 3 months) are shown for both groups. The dotted lines indicate the threshold of the minimal detectable change (MDC) or minimally clinically important difference (MCID) of each test. The correlation between the sensorimotor component of the Barcelona Music Reward Questionnaire (BMRQ) and the improvement in the ARAT at 3 months is shown for both groups.

For the cognitive outcomes, groups did not differ in the change scores from baseline to posttreatment (Table 4). However, when testing the within-group differences, participants in the MST-group improved in verbal learning of the RAVLT ($t(17) = -2.67, p < 0.05, d = 0.97$).

Table 4. Results for the secondary cognitive outcomes.

Neuropsychological test	MST-group			CT-group			Between-groups Baseline Post-test
	Baseline	Post-test	p	Baseline	Post-test	p	
Secondary cognitive outcomes							
Digit span	9.8 (3.3)	10.5 (3.3)	.185	9.8 (2.9)	10.1 (2.5)	.379	.520
Rey Auditory Learning Test							
<i>Learning</i>	8.5 (2.4)	9.7 (2.2)	.016	7.9 (2.4)	8.2 (2.6)	.500	.170
<i>Immediate recall</i>	5.8 (2.7)	6.7 (2.4)	.056	5.7 (2.2)	5.6 (2.2)	.847	.168
<i>Differed recall</i>	5.1 (2.6)	5.9 (2.5)	.078	5.6 (2.9)	5.6 (2.3)	1	.235
<i>Recognition</i>	11.5 (2.4)	12.3 (2)	.105	12.2 (1.9)	11.8 (2.6)	.521	.121
Story recall (Rivermead)							
<i>Immediate recall</i>	6.1 (2.8)	6 (2.6)	.940	4.8 (2.4)	5.5 (3.3)	.276	.364
<i>Differed recall</i>	4.3 (2.7)	4.6 (2.1)	.550	3.7 (1.9)	4.7 (2.2)	.062	.231
Stroop task	53.5 (8.8)	55.7 (5.6)	.159	49.4 (9.1)	51.9 (4.9)	.195	.905
Trail Making Test (Part A)	60.7 (26.3)	60.5 (30.2)	.949	66.8 (50.2)	61 (29.3)	.464	.519

The mean scores and standard deviations are shown for the secondary cognitive outcomes for both the MST and CT-groups at baseline and post-treatment (post-test). The dependent t -test for paired samples was used to test within-groups comparisons between baseline and post-test scores. The between-groups comparisons were analysed using independent t -tests with the change scores from baseline to post-test. Scalar punctuations are presented for the Digit span and the Stroop task. The Trail Making Test (Part A) is expressed in seconds. Some participants could not complete the Rey Auditory Verbal Learning Test (MST-group $n=18$ at baseline and post-test).

For the mood and QoL outcomes, the change score of the language domain of the Stroke-specific Quality of Life Scale was significantly different between groups ($t(35) = 2.96, p = 0.005, d = 0.20$) (Figure , Table 5 and Table 6). The MST-group improved in the language domain from baseline to posttreatment ($t(18) = -2.23, p = 0.039, d = 0.54$) while the CT-group did not show any improvement. There were no significant differences between groups in the change scores of the other tests assessing mood and QoL. The within-groups analyses in the MST-group showed a reduction in the fatigue-inertia component of the Profile of Mood States ($t(16) = 2.45, p = 0.026, d = 0.62$) and the negative affect measured with the Positive and Negative Affect Scale after the treatment ($t(16) = 2.25, p = 0.039, d = 0.64$) (Table 5). In this group, the overall score of the

Chapter 4. Study 2

Stroke-specific Quality of Life Scale ($t(18) = -2.66, p = 0.016, d = 0.64$) as well as the self-care ($t(18) = -3.44, p = 0.003, d = 0.80$) and productivity domains ($t(18) = -3.57, p = 0.002, d = 0.83$) improved after the therapy. Patients in the MST-group also presented an improvement in the physical and social function components of the Health survey questionnaire SF-36 ($t(16) = -2.24, p = 0.040, d = 0.54, t(16) = -3.70, p = 0.002, d = 0.90$) (Table 6). In the CT-group, only a significant difference was found for the self-care domain of the Stroke-specific Quality of Life Scale after the treatment ($t(17) = -3.95, p = 0.001, d = 1.04$).

Table 5. Results for the secondary mood outcomes.

Mood questionnaire	MST-group			CT-group			Between-groups Baseline Post-test
	Baseline	Post-test	p	Baseline	Post-test	p	
Secondary mood outcomes							
Tension-Anxiety (POMS*)	5.6 (6.8)	3.9 (5.2)	.290	8.1 (7.4)	7.8 (7.8)	.819	.437
Depression-Dejection (POMS)	8.4 (8.2)	7.5 (7.8)	.623	10.6 (7.1)	13.5 (11.8)	.158	.165
Anger-Hostility (POMS)	8.5 (9.3)	7.2 (7.1)	.430	9.8 (7.3)	11.7 (9.5)	.188	.138
Vigor-Activity (POMS)	14.6 (6.6)	14.8 (5.9)	.934	12.5 (6.8)	12.5 (6.3)	.975	.975
Fatigue-Inertia (POMS)	6.8 (4.7)	4.4 (3.6)	.026	7.6 (5.8)	8.2 (6.4)	.586	.052
Confusion-Bewilderment (POMS)	4.2 (5.9)	3.4 (5.5)	.396	4.3 (5.1)	4.5 (4.4)	.850	.429
Beck Depression Inventory Scale	10.2 (6.9)	8.8 (7.5)	.205	12.3 (8.5)	10.6 (9.1)	.291	.884
Positive Affect (PANAS*)	33.5 (9.5)	33.7 (9.3)	.865	31.5 (7.6)	30.3 (7.3)	.545	.561
Negative Affect (PANAS)	19.8 (9.2)	15.8 (4.9)	.039	21.2 (9)	20 (8.7)	.517	.270
Apathy Evaluation Scale	36.1 (7.2)	32.8 (10.4)	.066	34.3 (4.4)	35.7 (7.8)	.397	.053

The mean scores and standard deviations are shown for the secondary mood outcomes for both the MST and CT-groups at baseline and post-treatment (post-test). The dependent *t*-test for paired samples was used to test within-groups comparisons between baseline and post-test scores. The between-groups comparisons were analysed using independent *t*-tests with the change scores from baseline to post-test. Some participants could not complete the mood evaluation (MST-group $n=17$ at baseline and post-test for all questionnaires). *POMS, Profile of Mood States; PANAS, Positive and Negative Affect Scale.

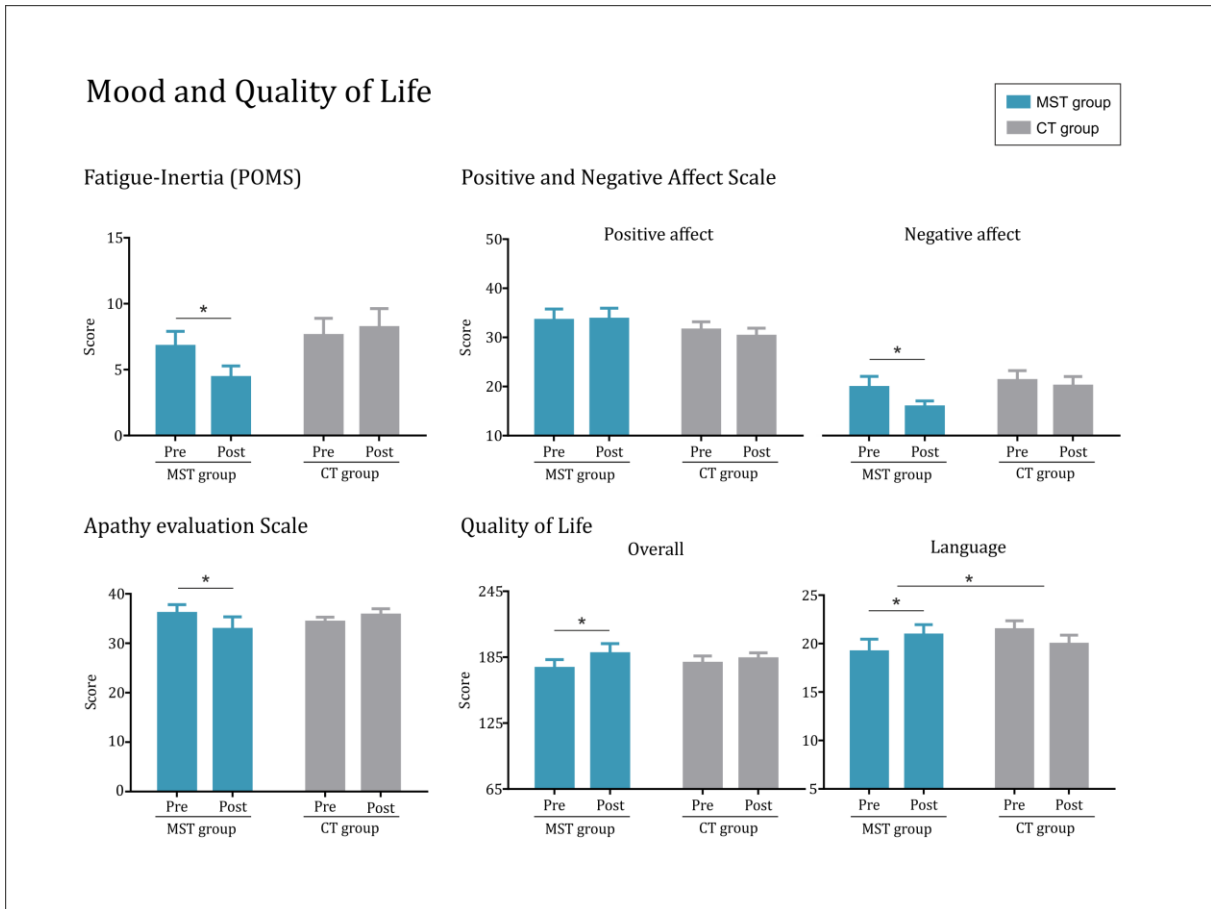


Figure 3. Results for the secondary mood and QoL outcomes.

Results for the fatigue-inertia component of the Profile of Mood States (POMS), the Positive and Negative Affect Scale, the Apathy Evaluation Scale, and the Stroke-specific Quality of Life Scale (overall and language domain) are shown for both groups. * $p < 0.05$.

Table 6. Results for the secondary QoL outcomes.

QoL questionnaire	MST-group			CT-group			Between-groups Baseline Post-test
	Baseline	Post-test	<i>p</i>	Baseline	Post-test	<i>p</i>	
Secondary QoL outcomes							
Stroke-specific Quality of Life Scale	174.6 (32.9)	185.9 (38.8)	.016	179.6 (27.7)	183.5 (23.4)	.517	.193
<i>Energy</i>	10.5 (2.7)	9.2 (3.4)	.088	8.6 (3.6)	8.8 (3.8)	.808	.190
<i>Family roles</i>	11.1 (2.5)	11.2 (3)	.754	10.3 (3.7)	10.6 (3.2)	.748	.903
<i>Language</i>	19.2 (5.7)	20.9 (4.6)	.039	21.4 (3.9)	19.9 (3.9)	.066	.005
<i>Mobility</i>	23.5 (5.2)	24.8 (5.7)	.095	21.8 (5.8)	23.1 (3.7)	.287	.978
<i>Mood</i>	20.1 (4.6)	20.1 (6.1)	.956	20.4 (5.4)	20.2 (4.5)	.839	.906
<i>Personality</i>	11.4 (3.6)	11.2 (4.1)	.795	11.4 (3.1)	11.3 (2.9)	.901	.965
<i>Self-care</i>	17.2 (3.7)	20.4 (4.7)	.003	18.5 (4.4)	21.7 (2.7)	.001	.994
<i>Social roles</i>	14 (6)	14.9 (6.5)	.481	13.2 (4.4)	12.9 (3.4)	.835	.495
<i>Thinking</i>	9.2 (4.1)	10.1 (4)	.362	10.9 (4.1)	10.1 (4.1)	.381	.206
<i>Upper extremity function</i>	17.5 (5.2)	19.6 (4.9)	.094	19.6 (4.4)	20.3 (3.4)	.381	.327
<i>Vision</i>	13.2 (2.8)	13.6 (2.3)	.249	14.6 (1.1)	14.6 (1)	1	.405
<i>Work and Productivity</i>	7.9 (3.6)	10 (3.3)	.002	8.9 (3.2)	10.1 (3.1)	.119	.337
Health survey questionnaire SF-36							
<i>Physical function</i>	46.2 (23.6)	55.3 (23.4)	.040	39.2 (20.1)	45 (21.9)	.293	.630
<i>Role limitations due to physical problems</i>	14.7 (28)	17.6 (32.8)	.773	17.1 (27.7)	23.7 (38.6)	.350	.762
<i>Pain</i>	61.1 (34.3)	56.7 (27.5)	.627	54 (36.5)	50.4 (33)	.670	.947
<i>General health</i>	55.3 (18.3)	61.1 (18.4)	.075	59.1 (21.4)	57.2 (22.7)	.599	.109
<i>Vitality</i>	55.9 (21.2)	60 (20.3)	.407	48.4 (21.9)	53.2 (26.8)	.354	.930
<i>Social function</i>	53.8 (26.1)	75.7 (27.5)	.002	54.7 (31.2)	64.7 (30.7)	.150	.194
<i>Role limitations due to emotional problems</i>	62.7 (48.4)	76.5 (40.4)	.275	70.5 (43.1)	70.2 (42.9)	.956	.286
<i>Mental health</i>	69.6 (17.8)	71.1 (21.2)	.737	61.7 (17.6)	66.3 (21.6)	.278	.587

The mean scores their standard deviations are shown for the secondary cognitive outcomes for both the MST and CT-groups at baseline and post-treatment (post-test). The dependent *t*-test for paired samples was used to test within-groups comparisons between baseline and post-test scores. The between-groups comparisons were analysed using independent *t*-tests with the change scores from baseline to post-test. Some participants could not complete the Stroke-specific Quality of Life Scale (CT-group n=18 at baseline and post-test) and the Health survey questionnaire SF-36 (CT-group n=17 at baseline and post-test).

4.3.4 Music reward experiences and response to Music-supported Therapy

A positive correlation was found between the improvement in ARAT at 3 months and the sensory-motor component of the Barcelona Music Reward Questionnaire for the MST-group ($r = 0.562, p = 0.024$) but not for the CT-group ($r = -0.305, p = 0.21$) (Figure 2). Patients in the MST-group with higher capacity to experience pleasure from musical activities (sensory-motor component) showed a major improvement in the ARAT at 3 months. Significant differences were observed between both correlations using the Fisher's z test ($z = 2.4, p < 0.05$).

4.4 Discussion

In this RCT, we examined the effectiveness of adding Music-supported Therapy to a rehabilitation program for subacute stroke patients and compared it to standard rehabilitation alone after controlling for the total duration of the intervention. Regarding our primary and secondary motor outcomes, no group differences were observed at the end of the treatment or at the 3-month follow-up. With regard to the mood and QoL secondary outcomes, a larger improvement in the MST-group was found for the language domain of the Stroke-specific Quality of Life Scale after treatment when compared with the CT-group. Importantly, in the MST-group, a significant association was encountered between patients' individual differences in their capacity to experience pleasure from engaging in musical activities and motor improvement (primary outcome at 3-month follow-up). This association was not present in the CT-group.

No superiority effect in adding Music-supported Therapy to a standard program of rehabilitation at the motor level was observed in the present trial. Both groups received the same standard program, and, in the CT-group, additional training was provided to compensate for the extra time that the MST-group received. As expected in the subacute stage, patients in both groups improved their motor deficits, showing an enhancement in dexterity, functional movements, and motor performance in activities of daily living. Our results differ from the study of Schneider and colleagues (2007) in which patients receiving Music-supported Therapy in addition to other standard rehabilitation techniques increased the speed and smoothness of movements as well as their overall motor function when compared with a control group (Schneider et al., 2007). In this study, the experimental and control group received around 13.5 hours of conventional rehabilitation within three weeks. In addition, the experimental group spent 30 min more per day (three weeks) undergoing Music-supported Therapy, but no extra rehabilitation time was provided to the control group. In our study, groups received nearly 40 hours of conventional rehabilitation during four weeks, and both the Music-supported Therapy and the CT-groups

were provided 30 min more per day of Music-supported Therapy or extra training with conventional therapies. Whereas the improvement of the MST-group is similar in both studies, the training intensity of the control group might explain the different results obtained in the two studies. An important aspect to consider for future trials is to what extent the Music-supported Therapy program might show larger effects when added to standard rehabilitation programs of shorter duration and intensity. Music-supported Therapy could boost motor improvement when fewer resources could be devoted to individualised conventional physiotherapy and occupational therapy programs after subacute stroke.

An outstanding finding in our study is that, in the MST-group, patients' intrinsic motivation to participate and enjoy musical activities (and in particular musical activities involving a strong sensorimotor component, e.g., tapping to the beat, humming, singing, or dancing) correlated with a larger improvement in the primary motor outcome at 3 months when compared with the CT-group. This result agrees with recent proposals in the field of motor learning highlighting the importance of motivational factors in motor skill learning (Wulf & Lewthwaite, 2016). Moreover, recent studies have highlighted the significant role of intrinsic motivation in successful learning, an effect mediated by midbrain dopaminergic pathways and their interaction with reward-memory circuits (Gruber, Gelman, & Ranganath, 2014; Ripollés et al., 2014, 2016). Music-supported Therapy training is adapted to patient's needs, providing exercises that challenge the patient but at the same time are achievable, promoting autonomy and giving patients control over the learning experience. This might reduce the perceived task difficulty, distracting attention from the effort required (Dyrlund & Wininger, 2008) and increase feelings of self-efficacy (Wulf & Lewthwaite, 2016). At the same time, during the Music-supported Therapy sessions, the therapist provides direct positive feedback about the patient's performance, reinforcing the learning experience. Taken together, these motivational aspects could influence motor skill learning in patients with higher reward sensitivity to music (Dayan & Cohen, 2011; Krakauer, 2006).

Although no difference was observed in the improvement at emotional level between the two groups, it is relevant to note that within-group analysis in the MST-group revealed a significant reduction in fatigue and negative affect and a better QoL after treatment. The CT-group only improved in the self-care QoL domain. Additionally, although there were no differences between groups at the cognitive level, the within-groups analyses showed that the MST-group improved their attention and verbal memory after the training. Similar findings have been previously described at the cognitive and emotional levels after Music-supported Therapy in chronic stroke patients (Ripollés et al., 2016; Rojo et al., 2011) as well as in other music programs for neurological population (François et al., 2015; Särkämö et al., 2008; Särkämö, Tervaniemi, et al.,

2014; Sihvonen et al., 2017). Thus, these results reinforce the capacity of music in therapeutic programs as a mood enhancer (Altenmüller & Schlaug, 2015).

The potential impact of music in stroke recovery fits with the recent findings of the EVREST trial, in which it was observed that recreational activities can be as effective as other sophisticated motor rehabilitation programs (Saposnik et al., 2016). Future studies should consider the intensity and duration of the standard rehabilitation program to which the Music-supported Therapy is added, as well as the dose-response of Music-supported Therapy (Grau-Sánchez, Ramos, Duarte, Särkämö, & Rodríguez-Fornells, 2017). Moreover, aspects influencing the overall recovery process, such as the lesion location, white matter damage, and the extent of deficits, should be taken into account. The Music-supported Therapy program could be modified by introducing new components, such as the self-selection of songs or musical styles, improvisation, music sonification (Scholz et al., 2016) and other types of feedback that are in line with the most advanced motor learning paradigms. Music-supported Therapy can also be adapted in order to be applied at home or in groups to incorporate more social aspects (Street, Magee, Odell-Miller, Bateman, & Fachner, 2015; Villeneuve, Penhune, & Lamontagne, 2014).

In this study, Music-supported Therapy in addition to the rehabilitation program did not show superiority over conventional therapies. Importantly, the patient's intrinsic motivation to engage in music activities should be taken into account, since we observed an association between motivation and motor improvement. In this sense, new questions arise in the design of more individualised rehabilitation programs, tailoring the activities or therapies provided in the rehabilitation centres to the interest of the patient.

Study 3

Chapter 5. Study 3

Neural plasticity induced by Music-supported Therapy in subacute stroke patients

5.1 Introduction

Rehabilitation to treat motor deficits after stroke aims to facilitate adaptive learning to achieve functional recovery (Carey, Polatajko, Connor, & Baum, 2012). The neural substrate that underpins functional recovery is brain plasticity, understood as the ability of the nervous system to adapt to injury by changing its structure, function and connections (Cramer et al., 2011). Two main forms of brain plasticity can manifest after stroke: endogenous plasticity and experience-dependent plasticity (Hyllin et al., 2017; Krakauer et al., 2012). Endogenous plasticity is driven by internally generated stimuli and is characterised by a period of increased excitability and the expression of growth-promoting genes in the initial weeks after the stroke (Carmichael et al., 2005; Krakauer et al., 2012; Schienu et al., 1996). These cellular processes enable the establishment of new connections and the reorganisation of cortical motor representations (Buma et al., 2013; Carmichael, 2006; Dancause & Nudo, 2011). Importantly, training is essential to induce cortical motor map reorganisation (Kitago & Krakauer, 2013; Krakauer et al., 2012; Nudo et al., 1996). Rehabilitation aims to modulate the endogenous plastic mechanisms and induce forms of experience-dependent plasticity through training and demanding and enriched environments (Zeiler & Krakauer, 2013).

After a stroke, it is well characterised that the disruption of the interhemispheric balance leads the non-lesioned hemisphere to increase its activity (Cicinelli et al., 2003; Duque et al., 2005; Murase et al., 2004). Stroke patients often exhibit a pattern of bilateral activations of motor regions when moving the affected hand (Carey et al., 2006; Cramer, Finklestein, Schaechter, Bush, & Rosen, 1999; Jaillard et al., 2005). At a system level, this can be understood as a form of compensation but also as functional dedifferentiation because ipsilateral motor pathways are non-specialised to sustain function of the paretic hand (Fornito et al., 2015; Netz et al., 1997). Several studies have highlighted the importance of inducing reorganisation within the lesioned hemisphere since a return to a more normal pattern of brain activations has been associated with better recovery (Cramer, 2008; Johansen-Berg, Dawes, et al., 2002; Ward, Brown, Thompson, & Frackowiak, 2003a). However, the bimodal-balance recovery model recently proposed by DiPino and colleagues (2014) suggests that hemispheric reorganisation is

determined by the amount of initial anatomical damage (Di Pino et al., 2014). In other words, intrahemispheric reorganisation depends on the amount of structural reserve in the affected hemisphere to support function. In stroke, one of the most important predictors of recovery is the integrity of the corticospinal tract, which determines whether the motor function is sustained, regained with time or lost (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Krakauer & Marshall, 2015; Puig et al., 2017; Stinear, 2010). Thus, the integrity of the corticospinal tract will influence whether reorganisation within the affected hemisphere can take place. Rehabilitative interventions should positively influence neural plasticity to promote adaptive changes in the affected hemisphere but taking into account that this may not be possible in patients with severe damage to white matter motor tracts (Di Pino et al., 2014).

Music-supported Therapy aims to improve the motor function and reduce motor deficits in stroke patients by promoting adaptive plastic mechanisms through motor skill learning (Rodríguez-Fornells et al., 2012; Schneider et al., 2007). Basic research has shown that learning to play an instrument leads to reorganisation of cortical motor maps (Lotze et al., 2003; Pascual-Leone et al., 1995; Schlaug, 2015). In this line, Music-supported Therapy aims at promoting similar plastic changes as those seen in healthy individuals when they learn to play an instrument (Rodríguez-Fornells et al., 2012). Previous studies have shown that Music-supported Therapy induces changes in the excitability of the sensorimotor cortex, cortical motor map reorganisation, and changes in brain function and connectivity in stroke patients (Amengual et al., 2013; Ripollés et al., 2016; Rojo et al., 2011). Specifically, Amengual and colleagues (2013) reported an increase of excitability in the affected sensorimotor cortex and a lateral shift in the cortical representation of the paretic hand in chronic stroke patients treated with Music-supported Therapy (Amengual et al., 2013). The same group of patients was evaluated before and after the intervention using functional Magnetic Resonance Imaging (fMRI, Ripollés et al., 2016). Before the intervention, patients exhibited bilateral activations of motor regions when moving the affected hand. Interestingly, ipsilateral activations were reduced after patients were treated with Music-supported Therapy, showing a pattern of intrahemispheric reorganisation within the lesioned hemisphere. Moreover, during a music listening task, activation of motor regions of the affected hemisphere, which were not present at baseline, were observed after the training, suggesting a reestablishment of the audio-motor coupling. An analysis of functional connectivity revealed that the supplementary motor area increased its functional connectivity with the primary auditory cortex and the precentral gyrus after Music-supported Therapy (Ripollés et al., 2016). Despite these promising findings, this study made use of an experimental design that did not have a control group of patients undergoing a different treatment. Therefore, it is unclear if these plastic mechanisms are specific of Music-supported Therapy and no direct

comparison has been made with other treatments. Moreover, the sample of this study was in the chronic stage, and thus, it is unknown if Music-supported Therapy promotes similar plastic changes in the subacute stage.

Addressing these questions and considering the recent models of hemispheric reorganisation, we evaluated a subsample of participants from Study 2 using a protocol of structural imaging and fMRI. The design of Study 2 was an RCT where two groups of treatment were established to test the effectiveness of adding Music-supported Therapy to the standard program of rehabilitation in subacute stroke patients. In the present study, we wanted to thoroughly describe the structural damage of the sample and investigate differences in the lesions' characteristics and white matter damage between groups at baseline. The idea behind this analysis was to explore that the observed behavioural changes in Study 2 were not influenced by differences in the patients' lesion. In addition, we tested if the integrity of the corticospinal tract at baseline was related to motor recovery, predicting a positive relationship between these two variables. Finally, we wanted to explore the mechanisms of brain plasticity induced by Music-supported Therapy in subacute stroke patients compared to conventional therapy. To this aim, we evaluated patients during a motor task with fMRI before and after the intervention. Our hypothesis was that patients in the Music-supported Therapy group would show a major reduction of bilateral activations after the training than patients treated with conventional therapy.

5.2 Methodology

5.2.1 Participants

For this study, a subsample of Study 2 was evaluated using an fMRI protocol before and after the treatment. Participants were subacute stroke patients who were undergoing an outpatient rehabilitation program at the Department of Physical Medicine and Rehabilitation at the Hospitals del Mar i de l'Esperança. As in Study 2, eligibility criteria were: (i) mild-to-moderate paresis of the upper extremity after a first-ever stroke, (ii) less than 6 months after the stroke, (iii) age between 30 and 75 years, (iv) no major cognitive deficits affecting comprehension (Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) > 24), (v) no neurological or psychiatric co-morbidity, (vi) no previous formal musical education, and (vii) ability to speak Spanish and/or Catalan. Mild-to-moderate paresis was defined as having a score between 2 and 4 in the Medical Research Council Scale for Muscle Strength (Medical Research Council, 1976) at the distal muscles of the upper extremity. An additional criterion was added to take part in this

study: (viii) no previous health condition incompatible with an MRI evaluation (i.e. pacemaker or claustrophobia).

Participants were given oral and written information about the MRI procedure and signed a consent form.

5.2.2 Design and treatment

Participants were randomised into two groups of treatment: a group receiving Music-supported Therapy (MST-group) and a group that was treated with extra time of conventional therapy (CT-group). In both groups, 20 sessions of 30 minutes of training were provided during four weeks. All participants were undergoing a standard program of rehabilitation for subacute stroke that consisted of two daily hours of physical and occupational therapy (for a detailed description of procedures regarding the design and intervention, see Methodology section in Study 2, Grau-Sánchez et al., 2018).

Before and after the four-week training, an MRI evaluation was performed to obtain structural and functional images and study plastic changes associated with the intervention in stroke patients.

5.2.3 Data acquisition

A 3 T whole-body MRI scanner (Siemens Magnetom Trio, Hospital Clinic, Barcelona) was used to acquire structural [magnetization-prepared, rapid-acquired gradient echoes (MPRAGE), 240 slices, TR=2300 ms, TE=3 ms, 1 mm isotropic voxels] and functional (echo planar T2*-weighted gradient echo sequence, TR= 2000 ms, TE = 29 ms, slice thickness =4 mm, 3.5× 3.5 mm in-plane resolution, no gap) images. For the functional images, 176 volumes were acquired during a motor task. These volumes were comprised of 32 axial slices aligned to the plane intersecting the anterior and posterior commissure. Visual instructions and stimuli during the motor task were displayed using the Presentation software (<http://www.neurobs.com>), and participants wore MRI-compatible goggles and headphones to visualise stimuli and reduce scanner noise.

5.2.4 Lesion analysis

For each patient, a binary mask of the lesion was drawn in native space using the high-resolution structural T1 image with the software 3D Slicer (<http://www.slicer.org>; Fedorov et al., 2012). Lesion masks were created by a research assistant with a background in neuroanatomy who

depicted the lesion boundary taking into account information from each participant's medical record. Lesion masks were later revised by a neuroradiologist.

The lesion masks were used to (i) characterise the sample, (ii) study the relationship between the integrity of the corticospinal tract and motor recovery, and (iii) preprocess functional images.

5.2.4.1 Lesion description and sample characterisation

To characterise the sample, lesion masks of the MRI pre-intervention session were normalised to the MNI space. Firstly, an overlap map was created by adding the participants' lesion masks. For this overlap map, the lesion masks of patients with right hemisphere strokes were flipped in the mid-sagittal plane so all the patients would have the lesion on their left hemisphere. Secondly, for each patient, an image was created by adding the flipped lesion mask and a reconstruction of the corticospinal tract (Rojkova et al., 2016). Thirdly, the software Tractotron (BCBtoolkit, <http://www.toolkit.bcblab.com>; Foulon et al., 2018) was used to estimate the severity of white matter tract disconnection. This software contains a reconstruction of white matter pathways from a healthy sample (Rojkova et al., 2016) and provides a probability of disconnection for all white matter tracts induced by a lesion at the individual level (Thiebaut De Schotten et al., 2014). Above a probability of disconnection of 50%, it is considered that a white matter tract is disconnected. For this analysis, lesion masks were not flipped. We considered the most relevant frontal tracts and calculated the number of patients in each group who had a given tract affected. Between-group differences in the distribution of affected tracts were evaluated with the Pearson χ^2 test.

5.2.4.2 Relationship between the integrity of the corticospinal tract and motor recovery

The Tractotron software also offers a value for the proportion of disconnection, which is calculated as the number of damaged voxels in a tract divided by the volume of the tract (Foulon et al., 2018). We studied the relationship between white matter damage in the corticospinal tract and the amount of improvement in the primary outcome (Action Research Arm Test). Correlations were computed in order to study the relationship between these two variables in the overall sample and then separately in each group to test for between-group differences.

5.2.5 Experimental design

The motor task consisted of sequential index and middle finger tapping movements using a block design. There were eight active blocks of 20 seconds of finger movements (4 active blocks per hand) and eight blocks of 20 seconds of rest. Participants had to perform a sequential tapping movement with the index and middle finger of either the right or left hand during the active blocks. Between these active blocks, rest blocks were introduced (ABCB design, where A corresponds to movements with the right hand, B to rest, and C to movements with the left hand). Participants held a response pad in each hand, which had two response buttons to press alternately, one for the index finger and the other one for the middle finger. Before the MRI evaluation, participants were instructed in this task and performed a practice block to ensure the understanding of cues. Inside the scanner, visual stimuli were displayed on a screen that participants were able to see through the goggles. These visual stimuli consisted of cues to perform the sequential tapping movements with the right or left hand or to rest. Figure 1 illustrates the cues for the motor task. Response pads were connected to LEDs, allowing the monitoring of task performance by a research assistant who was outside the scanner.

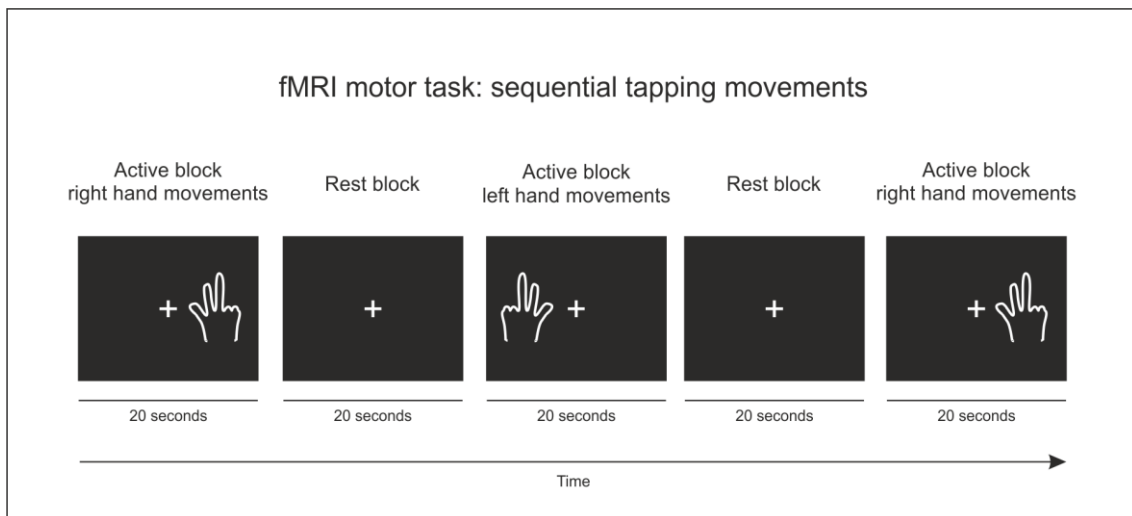


Figure 1. Motor task for the fMRI protocol.

In this task, participants had to perform sequential tapping movements with the index and middle finger of either the right (active block, right hand movement) or the left hand (active block, left hand movement). There were eight active blocks (4 active blocks per hand), and rest blocks were introduced in between. Each block had a duration of 20 seconds.

5.2.6 fMRI data analysis

Functional images were analysed with the Statistical Parameter Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, University College, London, UK,

<http://www.fil.ion.ucl.ac.uk/spm>). Images were realigned, segmented, normalised and smoothed (8mm Gaussian Kernel) as part of the preprocessing. For the segmentation, unified segmentation (Ashburner & Friston, 2005) with medium regularisation and the participant's lesion mask were applied to obtain registration parameters for the normalisation of structural and functional images to MNI space (Brett, Leff, Rorden, & Ashburner, 2001).

Statistical evaluation of functional images was based on a least-square estimation using the general linear model, which included the lesioned areas (Friston et al., 1995). The different conditions of the task (movements of the right or left hand, or rest) were modelled with a box-car regressor waveform convolved with a canonical hemodynamic response function. A high-pass filter (to a maximum of 1/128 Hz) was applied to the data, and serial autocorrelations were estimated using an autoregressive model. A block-related design matrix was created with the mentioned conditions. After estimating the model, two main contrasts were calculated: movements of the right hand vs. rest and movements of the left hand vs. rest.

For each participant, the laterality of lesion was considered, and for those patients with right hemispheric lesions, contrasts were flipped so for all the patients the affected hand would be the right and the unaffected the left one (affected hemisphere= left, unaffected hemisphere= right). The flipped contrasts were coregistered with an image that was not flipped from a participant with a lesion in the left hemisphere. Thus, for the entire sample, the contrasts obtained from the first level analysis were renamed as: movements of the affected hand vs. rest and movements of the unaffected hand vs. rest.

First level contrasts were used for a flexible factorial ANOVA, which had two factors, Group (Music-supported Therapy or Conventional Therapy) and Evaluation time-point (pre- or post-intervention). This analysis was computed twice: once for the affected hand vs. rest and another one for the unaffected hand vs. rest. The results were restricted to four ROIs including (i) superior and middle temporal gyri and Heschl gyrus, (ii) inferior and middle frontal gyrus, (iii) supplementary motor area, and (iv) precentral and postcentral gyri of both hemispheres as these regions have been reported to be involved in audio-motor coupling (Bangert et al., 2006; Lahav, Saltzman, & Schlaug, 2007; Zatorre et al., 2007). The toolbox *Wfu pickatlas* (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) was used to create the ROIs. The results are reported at an uncorrected $p < 0.005$ threshold with 20 voxels of cluster extent. The Automated Anatomical Labelling Atlas (Tzourio-Mazoyer et al., 2002) included in the *xjView* toolbox (<http://www.alivelearn.net/xjview8>) was used to identify anatomical areas.

5.3 Results

5.3.1 Demographic and clinical characteristics

From the initial sample recruited in Study 2 (MST-group n=19; CT-group n=20), four participants in the MST-group and two in the CT-group did not undergo the MRI evaluation protocol due to previous health conditions that were incompatible with MRI. Moreover, in the preprocessing of images, we noticed that the quality of images from one participant in the MST-group and three in the CT-group were not good enough to be included in the analysis. Thus, for this study, we ended up having a sample of fourteen participants in the MST-group and fifteen participants in the CT-group. There were no significant differences in demographic and clinical variables between groups at baseline (Table 1). A detailed clinical description of participants is provided in Table 2.

Table 1. Demographic and clinical variables for both groups at baseline.

	MT group (n=14)	CT-group (n=15)	p-value
Demographic variables			
Age (range)	59.2 (45-74)	61.7 (49-70)	.386
Gender			
<i>Females (%)</i>	5 (35.7)	6 (40)	.812
<i>Males (%)</i>	9 (64.3)	9 (60)	
Clinical variables			
Stroke aetiology			
<i>Ischaemic (%)</i>	14 (100)	13 (86.7)	.156
<i>Haemorrhagic (%)</i>	0 (0)	2 (13.3)	
Lesion location			
<i>Cortical (%)</i>	4 (28.6)	3 (20)	.589
<i>Subcortical (%)</i>	11 (78.6)	12 (80)	.924
<i>Brainstem (%)</i>	2 (14.3)	3 (20)	.683
<i>Cerebellum (%)</i>	1 (7.1)	0 (0)	.292
Time since stroke (range)	62.2 (32-155)	66.9 (34-136)	.718
NIHSS* (range)	4.9 (2-8)	5.1 (2-8)	.755
Modified Rankin Scale (range)	3.4 (3-4)	3.1 (2-4)	.214
FMA* baseline (range)	46.4 (24-65)	44.9 (21-57)	.751
Rehabilitation received before enrollment			
Physiotherapy	23.5 (15.1)	15.8 (12.5)	.159
Occupational Therapy	20.1 (14.3)	18.7 (17.6)	.816
Speech therapy	11 (11.8)	15.5 (7.7)	.660
Reward in musical activities			
Barcelona Music Reward Questionnaire	72.5 (11.4)	69.4 (14)	.513

Absolute frequencies are shown for the variables gender, stroke etiology and lesion location. For the rest of variables the mean and standard deviation are shown except indicated otherwise. The differences between groups were evaluated with *t*-test for independent samples for quantitative variables and the Pearson χ^2 test for nominal ones. *NIHSS, National Institutes of Health Stroke Scale; FMA, Fugl-Meyer Assessment of Motor Recovery after Stroke; $p < 0.05$.

Music-supported Therapy group (MST-group)

Age	Gender*	Etiology*	Laterality *	Lesion location	Lesion size	NIHSS*	mRS*	Time since stroke	Level of motor impairment
60	F	I	L	Precentral and postcentral gyrus.	9034	5	3	39	24
73	M	I	R	Pons.	569	5	4	82	33
45	F	I	L	Caudate and lenticular nuclei, and internal capsule.	4470	5	4	39	65
58	M	I	R	Middle and inferior frontal gyrus, precentral and postcentral gyrus and insula.	44081	3	3	46	62
61	M	I	R	Insula, frontal and parietal lobes.	139987	5	3	61	45
64	F	I	L	Frontal, parietal, temporal and occipital lobes.	16580	8	4	121	29
60	M	I	R	Pons.	890	8	4	76	41
55	M	I	L	Corona radiate.	1827	4	3	33	65
56	M	I	L	Lenticular nucleus and internal capsule.	4873	6	3	55	29
59	M	I	L	Internal capsule.	6857	5	3	32	63
46	F	I	R	Frontal and parietal lobes, globus pallidus and internal capsule.	10083	2	3	34	58
57	M	I	L	Cerebellar hemisphere.	38266	4	3	50	57
62	F	I	R	Caudate and lenticular nuclei, and internal capsule.	10650	3	4	49	35
74	M	I	L	Internal capsule.	155	6	4	155	45

Conventional Therapy group (CT-group)										
Age	Gender*	Etiology*	Laterality*	Lesion location	Lesion size	NIHSS*	mRS*	Time since stroke	Level of motor impairment	
52	F	H	R	Lenticular nucleus, internal capsule and thalamus.	2428	6	4	97	55	
69	F	I	R	Caudate and lenticular nuclei, and internal capsule.	2388	6	4	63	41	
52	M	I	L	Internal capsule and thalamus.	1328	3	3	49	50	
63	F	I	R	Frontal and temporal lobes, insula.	44398	8	3	60	57	
65	M	I	R	Pons.	753	7	4	80	21	
56	M	I	L	Corona radiate.	297	5	4	39	46	
65	M	I	L	Caudate and lenticular nuclei.	3218	5	3	135	39	
49	M	I	L	Pons.	821	4	2	34	43	
63	F	I	L	Lenticular nucleus, internal capsule and thalamus.	2228	6	3	59	30	
59	M	I	R	Anterior cingulate gyrus.	1983	3	2	36	47	
70	F	I	R	Internal capsule.	5332	5	3	60	53	
70	M	I	L	Semioval center and caudate and lenticular nuclei.	1720	5	4	136	38	
60	F	H	R	Caudate and lenticular nuclei, internal capsule, and corona radiata.	49245	5	3	52	49	
67	M	I	R	Frontal and parietal lobes, caudate and lenticular nuclei and corona radiata.	6525	4	3	41	55	
66	M	I	L	Pons.	1767	8	3	63	51	

Table 2. Clinical description of participants.

*F, female; M, males; H, haemorrhagic; I, ischaemic; R, right; L, left; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. Lesion size is expressed in mm³, time since stroke is in days and the level of motor impairment is the Fugl-Meyer Assessment of Motor Recovery after Stroke score at baseline.

5.3.2 Lesion analysis

5.3.2.1 Lesion description and sample characterisation

As outlined in Table 1 and Table 2, most participants had lesions at the subcortical level, affecting the caudate and lenticular nuclei, internal capsule, thalamus and insula. Four patients in the MST-group and three in the CT-group had lesions that included cortical regions of the frontal, parietal and occipital lobes. Figure 2 is the overlap map that resulted from adding the lesion masks of each participant.

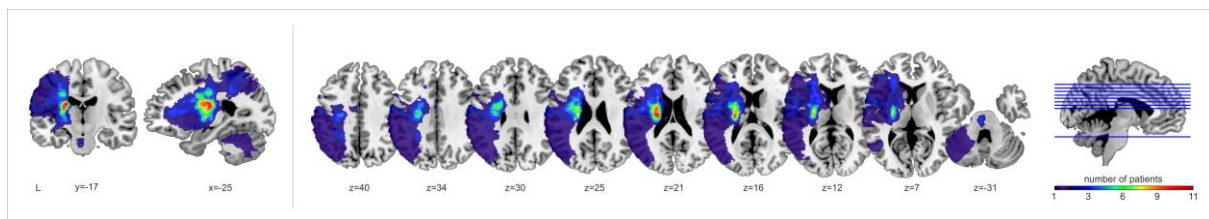


Figure 2. Lesion overlap map for all participants.

Warmer areas indicate greater lesion overlap, with a maximum overlap of 11 (total participants $n=29$). The patients' lesions were primarily distributed in the caudate and lenticular nuclei, internal capsule, thalamus and insula as well as in cortical regions of the frontal, parietal and occipital lobes. Fewer patients had lesions in the brainstem and cerebellum. Right-hemisphere lesions were flipped.

Figure 3 displays each participant's lesion and a reconstruction of the corticospinal tract as well as the amount of overlap between the lesion and the tract. Since all participants had motor deficits of the upper extremity, the lesion overlapped with the corticospinal tract as expected, except for one participant in the MST-group (P12), who had a lesion in the cerebellum.

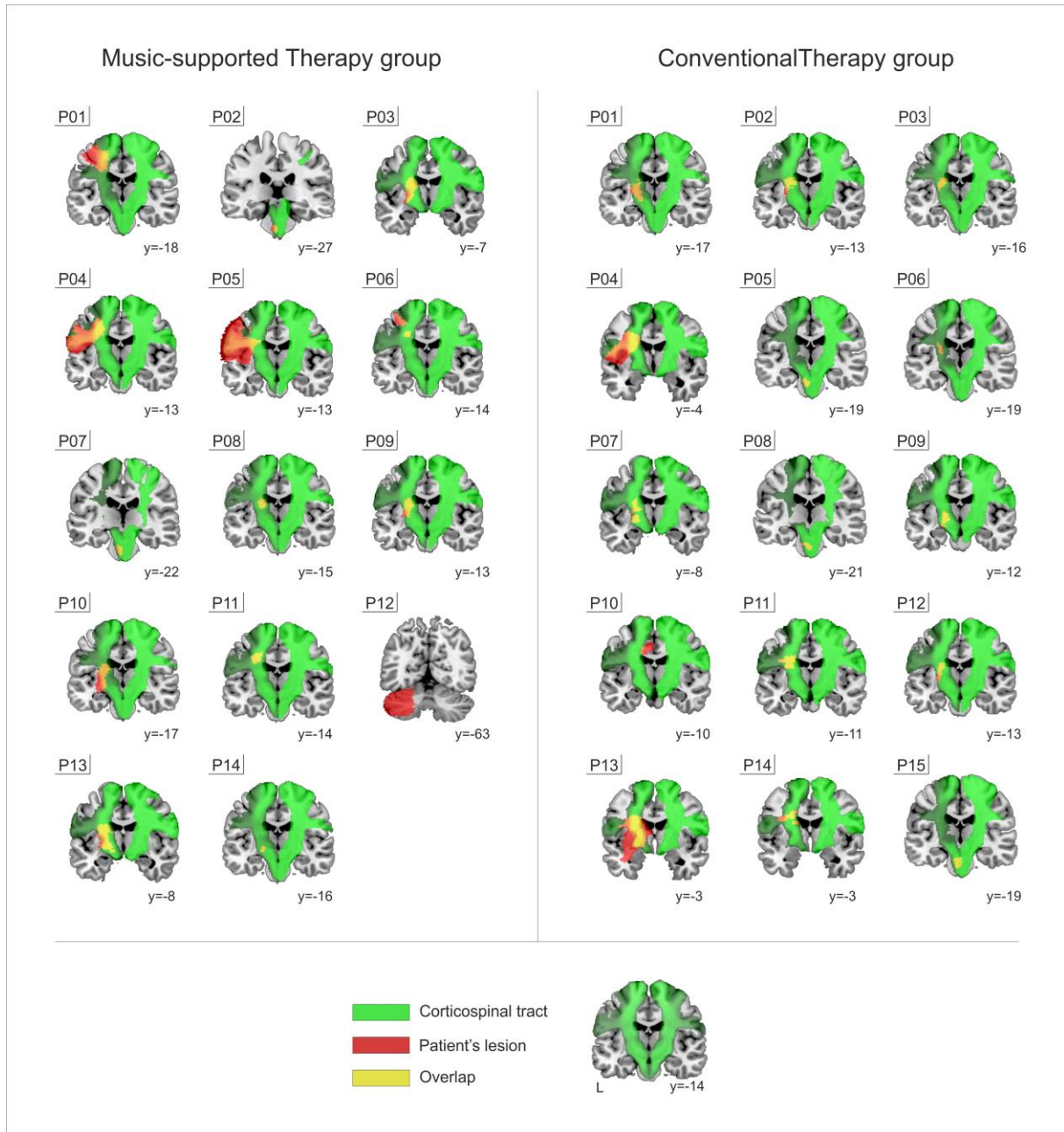


Figure 3. Lesion overlap with the corticospinal tract.

For each group, the lesion of each participant is shown in red. Both corticospinal tracts (left and right) have been added in green. The overlap between the patients' lesions and the corticospinal tract is shown in yellow. Right-hemisphere lesions were flipped to the left.

The results from the analysis of the probability of white matter tract disconnection are outlined in Table 3. There were no significant differences between groups in the distribution of participants who had a high probability of having a given tract affected for all the frontal tracts analysed. Both groups had a high probability of tract disconnection in the superior longitudinal fasciculus II and III, the corticospinal tract, the anterior thalamic radiations, and fronto-striatal and -pontine projections. There was a high probability of the frontal aslant tract of being disconnected in nearly 60% of participants in the MST-group.

Table 3. White matter damage for both groups at baseline.

	MST-group (n=14)	CT-group (n=15)
Frontal association tracts		
<i>Superior longitudinal fasciculus I</i>	5 (35.7)	3 (20)
<i>Superior longitudinal fasciculus II</i>	9 (64.3)	8 (53.3)
<i>Superior longitudinal fasciculus III</i>	10 (71.4)	9 (60)
<i>Cingulum - anterior</i>	4 (28.6)	3 (20)
<i>Arcuate fasciculus - anterior segment</i>	4 (28.6)	5 (33.3)
<i>Arcuate fasciculus - long segment</i>	7 (50)	5 (33.3)
<i>Arcuate fasciculus - posterior segment</i>	2 (14.3)	1 (6.7)
<i>Frontal commissural tract</i>	6 (42.9)	6 (40)
Frontal projection tracts		
<i>Corticospinal tract</i>	13 (92.9)	15 (100)
<i>Anterior thalamic radiations</i>	11 (78.6)	12 (80)
<i>Fronto-striatal projections</i>	10 (71.4)	12 (80)
<i>Fronto-pontine projections</i>	14 (100)	15 (100)
Frontal U-shaped tracts		
<i>Hand U tract*</i>	5 (35.7)	3 (20)
<i>Frontal aslant tract</i>	8 (57.1)	6 (40)
<i>Frontal superior longitudinal tract</i>	5 (35.7)	1 (6.7)
<i>Frontal inferior longitudinal tract</i>	2 (14.3)	4 (26.7)

Results of the probability of disconnection of frontal association tracts, frontal projection tracts and frontal U-shaped tracts for each group. Values indicate the number of participants who have damage in a given tract and the frequency within the group. For the Hand-U tract, the superior, middle and inferior U tracts have been grouped together in one variable. There were no statistical differences between groups in the distribution of affected tracts as evaluated with the Pearson χ^2 test.

5.3.2.2 Relationship between white matter damage and behavioural outcomes

The amount of white matter damage in the corticospinal tract, measured with the proportion of disconnection obtained from the Tractotron analysis, and improvement in the Action Research Arm Test was not correlated at a group level or when testing groups separately.

5.3.3 fMRI results

Participants performed a motor task inside the scanner that consisted of sequential tapping movements with the index and middle finger of either the unaffected or the affected hand. At baseline, the contrast movements of the unaffected hand vs. rest revealed activation of the supplementary motor area, the precentral and postcentral gyri, and the superior temporal gyrus of the contralateral hemisphere in both groups (Figure 4). Moreover, regions of the middle and superior frontal gyri ipsilateral to movement were active as well. In the CT-group, small portions of the precentral and postcentral gyri of the ipsilateral hemisphere were also active. A two-sample *t*-test for independent samples revealed that the CT-group had greater activation than the MST-group in the superior temporal gyrus (Brodmann area 22 and 42) of the affected hemisphere at baseline [$t(27) = 3.36$; $p < 0.005$; 25 voxels; MNI coordinates, $x = -66$ $y = -36$ $z = 18$] (Table 4, Figure 4). After the intervention, participants in the MST-group had greater activation in the middle temporal gyrus (Brodmann area 39) and insula of the ipsilateral hemisphere (affected hemisphere) while no differences were found for the CT-group [significant 2 (Group) \times 2 (Evaluation time-point) interaction: $t(27) = 4.07$; $p < 0.005$; 161 voxels; MNI coordinates, $x = -56$ $y = -66$ $z = 4$ for the middle temporal gyrus and $t(27) = 3.28$; $p < 0.005$; 49 voxels; MNI coordinates, $x = -50$ $y = -36$ $z = 18$ for the insula] (Figure 5). A post-hoc analysis for dependent samples showed that the MST-group had greater activation in the superior temporal gyrus after the intervention [$t(27) = 3.57$; $p < 0.005$; 133 voxels; MNI coordinates, $x = -52$ $y = -40$ $z = 16$] (Table 4, Figure 4).

For the affected hand and before the intervention, participants showed a pattern of bilateral activations of motor regions involving the supplementary motor area, and the precentral and postcentral gyri of both hemispheres (Figure 4). In the CT-group, small portions of the middle frontal gyrus contralateral to the movement were observed as well. Although participants in the CT-group seemed to have greater activation at baseline, no statistical differences between groups were found.

Table 4. fMRI results for a motor task.

Anatomical area	Coordinates	Size	t-value
CT-group > MST-group at baseline; Unaffected hand			
L Superior temporal gyrus	-66 -36 18	25	3.36
2 (Group) x 2 (Evaluation time-point); Unaffected hand			
L Middle temporal gyrus	-56 -66 4	161	4.07
L Insula	-50 -36 18	49	3.28
MST-group Post > Pre Intervention; Unaffected hand			
L Superior temporal gyrus	-52 -40 16	133	3.57
2 (Group) x 2 (Evaluation time-point); Affected hand			
L Middle temporal gyrus	-58 -4 -4	53	3.33
L Middle temporal gyrus	-64 -22 -12	38	3.94
MST-group Post > Pre Intervention; Affected hand			
L Superior temporal gyrus	-54 -18 -4	22	3.07

Anatomical areas where significant activations were found are reported. Results are reported at an uncorrected $p < 0.005$ threshold with 20 voxels of cluster extent. MNI coordinates are used. L, Left.

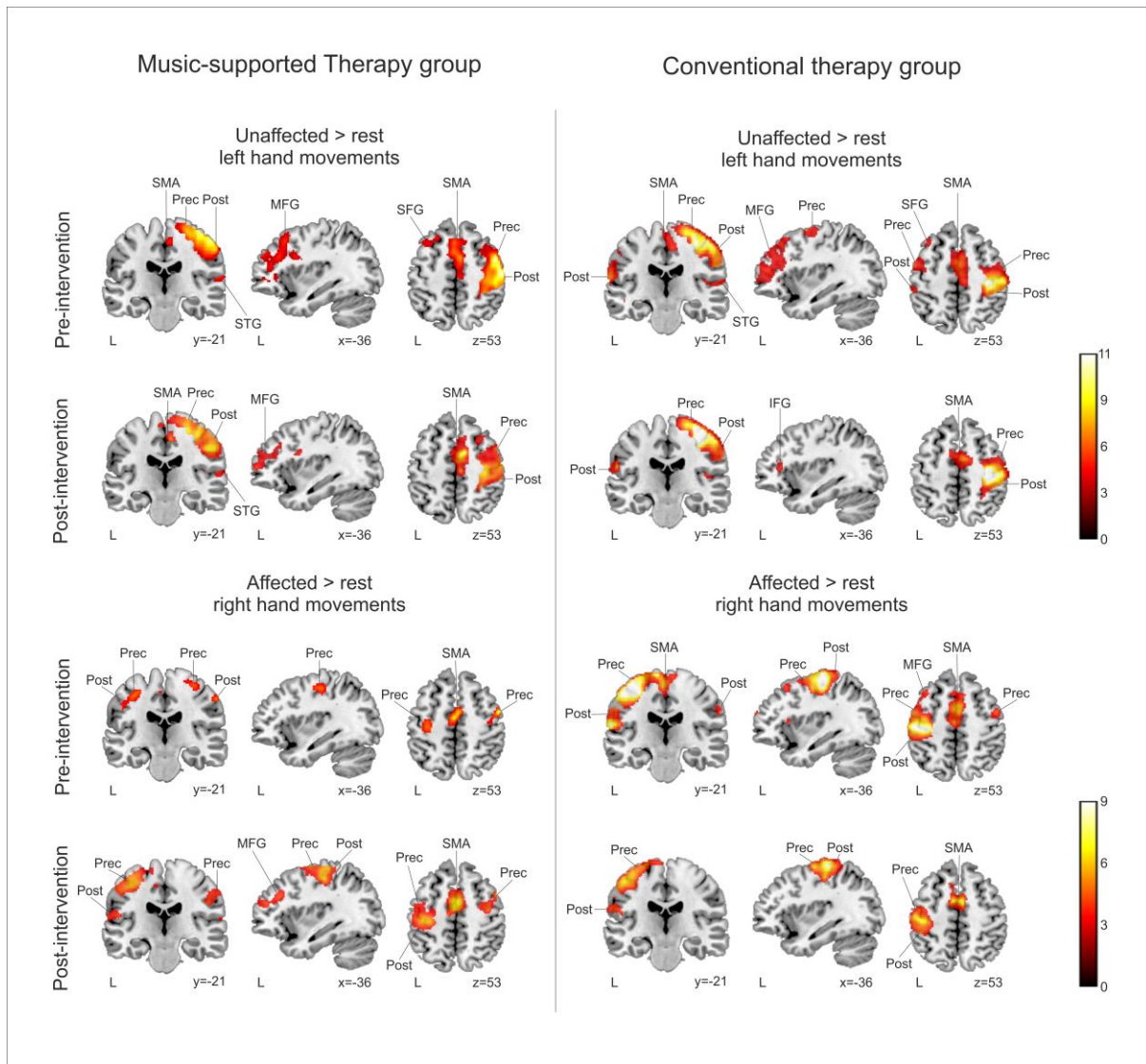


Figure 4. Activations during a motor task for both groups before and after the intervention.

Results of a motor task for both groups (MST-group, CT-group) and both the unaffected (right hand movements vs. rest) and the affected hand (left hand movements vs. rest) before and after the intervention. The motor task consisted of sequential tapping movements with the index and middle finger. Results are reported at an uncorrected $p < 0.005$ threshold with 20 voxels of cluster extent. MNI coordinates are used. Data from patients with right hemispheric lesions were flipped to the left. L, Left; SMA, Supplementary motor area; Prec, Precentral gyrus; Post, Postcentral gyrus; STG, Superior temporal gyrus; MFG, Middle frontal gyrus; SFG, Superior frontal gyrus; IFG, inferior frontal gyrus.

After the therapy, participants in the MST-group had greater activation in the middle temporal gyrus of the affected hemisphere [significant 2 (Group) \times 2 (Evaluation time-point) interaction: $t(27) = 3.33$; $p < 0.005$; 53 voxels; MNI coordinates, $x = -58$ $y = -4$ $z = -4$] (Table 4, Figure 5). Post-hoc analyses revealed that the MST-group showed more activation in the superior temporal gyrus (Brodmann area 22) after the therapy [$t(27) = 3.07$; $p < 0.005$; 22 voxels; MNI coordinates, $x = -54$ $y = -18$ $z = -4$] (Table 4, Figure 4). There were no significant differences in the CT-group due to the intervention.

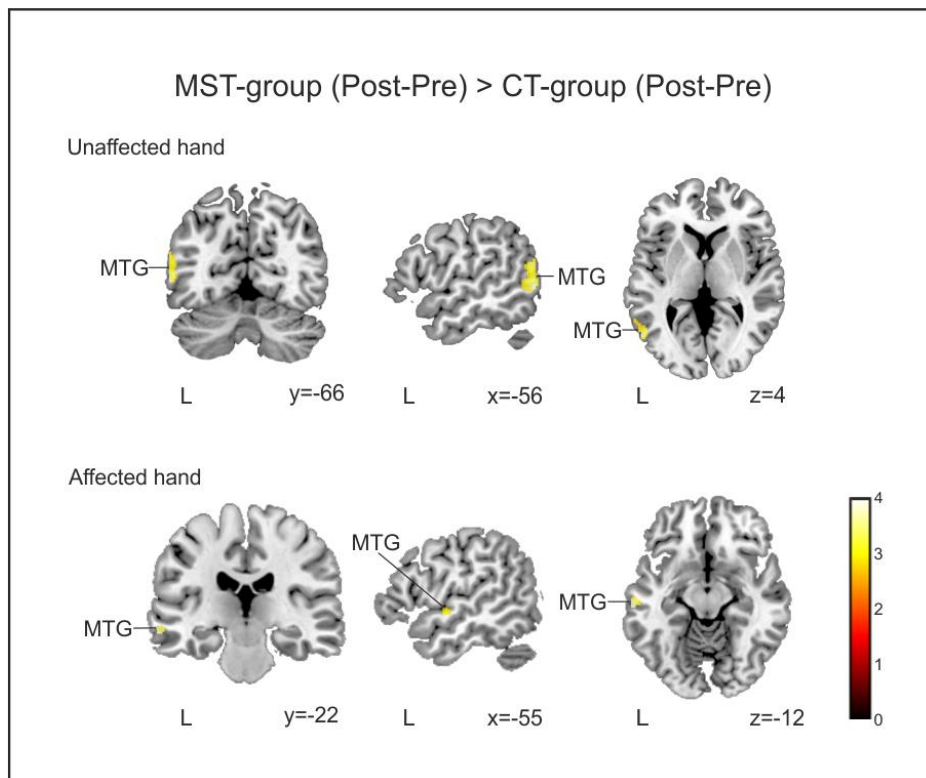


Figure 5. fMRI results for the interaction between groups and evaluation time-point.

Results of a motor task from the interaction between groups (MST-group, CT-group) and evaluation time-point (Pre- and post-intervention) for the unaffected and affected hand. The motor task consisted of sequential tapping movements with the index and middle finger. Results are reported at an uncorrected $p < 0.005$ threshold with 20 voxels of cluster extent. MNI coordinates are used. Data from patients with right hemispheric lesions were flipped to the left. L, Left; MTG, Middle temporal gyrus; STG, Superior temporal gyrus.

5.4 Discussion

This study evaluated a subsample from Study 2, which was an RCT that tested the effectiveness of Music-supported Therapy as an add-on treatment in the rehabilitation of motor deficits after stroke (Grau-Sánchez et al., 2018). The results of the RCT showed that, for the behavioural motor outcomes, there were no differences between Music-supported Therapy and conventional rehabilitation. In the present study, we aimed to (i) thoroughly characterise the lesions and white matter damage of participants in each group, (ii) test the relationship between the integrity of the corticospinal tract and the amount of motor recovery, and (iii) investigate the plastic mechanisms induced by each therapy.

Regarding the characterisation of samples, we observed that, apart from having two samples that did not differ in the main demographic and clinical variables, lesions and white matter damage was very similar between groups as well. In both groups, lesions were mainly located at

the subcortical level, and no differences were encountered in the distribution of the patient's lesion location. Moreover, all patients had damage in the corticospinal tract, except from one patient in the MST-group who had a lesion in the cerebellum that did not overlap with the corticospinal pathway. Still, this patient presented motor deficits because the cerebellum has direct projections to the corticospinal tract in its path at the brainstem level (Koziol et al., 2014). Regarding other tracts that might be relevant for the motor function such as frontal association and projections tracts and frontal U-shaped tracts, there were no differences between groups in the distribution of patients with damage to these tracts. In both groups, the majority of patients had damage to the superior longitudinal fasciculus II and III, the anterior thalamic radiations and fronto-striatal and –pontine projections. Overall, it can be concluded that both groups of patients were comparable at the neural level. In Study 2, we had already tested between-groups differences in the main clinical and demographic variables. The study of the lesion location and white matter damage reinforces the behavioural results obtained in the RCT since potential confounders regarding the patients' lesion are well controlled. Furthermore, providing a throughout characterisation of the sample might be of clinical relevance to support the generalisation of results to the stroke population (Bernhardt, Borschmann, et al., 2017; Logroscino, Capozzo, Tortelli, & Marin, 2016).

When we studied the relationship between the amount of damage in the corticospinal tract and motor recovery, measured with the Action Research Arm Test, we did not find any correlation between these two variables in the overall sample or when studying groups separately. The integrity of the corticospinal tract is one of the most important predictors of recovery (Krakauer & Marshall, 2015; Stinear, 2010). Moreover, according to the bimodal-balance recovery model, the structural reserve of the corticospinal tract would determine if reorganisation occurs in the affected or unaffected hemisphere (Di Pino et al., 2014). Traditionally, reorganisation within the affected hemisphere has been linked to better functional outcomes whereas patients with poor recovery usually show a greater involvement of the unaffected hemisphere (Cramer, 2008; Jaillard et al., 2005; Johansen-Berg, Dawes, et al., 2002; Murase et al., 2004). Therefore, the amount of damage to the corticospinal tract is linked to behavioural motor outcomes. Despite all this evidence, and contrary to what we expected, we did not find any relationship between corticospinal tract damage and motor recovery. One possible explanation might be the methodological limitations to estimate the proportion of disconnection. The proportion of disconnection was calculated as the number of damaged voxels in the tract (Foulon et al., 2018). The number of damaged voxels resulted from the overlap of normalised lesion masks with a reconstruction of the corticospinal tract from a healthy sample (Rojkova et al., 2016). The normalisation of lesions' masks can induce deformations in the shape of lesions and other analysis such as tractography, where white matter pathways can be reconstructed at the

individual level, might be more appropriate to study the relationship between behavioural outcomes and damage to relevant white matter pathways.

We studied the plastic mechanisms induced by the therapy with a motor task in an fMRI protocol. In this task, participants had to perform sequential tapping movements with the index and middle finger of either the affected or unaffected hand. When moving the unaffected hand, groups differ in the activation at baseline, having the CT-group greater activation in the superior temporal gyrus of the affected hemisphere, specifically in the auditory associative cortex (Brodmann area 22 and 42). Groups did not differ in the pattern of activations associated with movements of the paretic hand at baseline. After the intervention, the MST-group had major activations in the insula, and middle and superior temporal gyri than the CT-group when moving both the affected and unaffected hand. Therefore, the only difference between groups was greater activation of temporal areas in the affected hemisphere of the MST-group after the training. However, the results when studying movements of the unaffected hand pointed out that there were differences at baseline in the activation of these regions between groups. In this analysis, we expected that patients in the MST-group would show a greater pattern of intrahemispheric reorganisation within the lesioned hemisphere given that the Music-supported Therapy aims at inducing an enlargement and reorganisation of cortical motor maps (Amengual et al., 2013; Rodriguez-Fornells et al., 2012). The idea behind Music-supported Therapy is to promote the same changes as those seen in healthy participants when they learn to play an instrument, where the recruitment of adjacent cortical areas takes place (Pascual-Leone et al., 1995; Rodriguez-Fornells et al., 2012). Reorganisation within the affected hemisphere might be more adaptive because neural pathways are more efficient and specialised in moving the contralateral hand (Di Pino et al., 2014). In this line, previous studies have shown that patients treated with Music-supported Therapy show reduced bilateral motor activations after the training (Ripollés et al., 2016). Aside from the results observed in the temporal lobe, we did not find differences in the reorganisation of motor regions between groups. Future studies should consider evaluating the role of the auditory feedback with fMRI or conduct functional connectivity analysis to explore which are the specific changes induced by Music-supported Therapy at a system level.

Study 4

Chapter 6. Study 4

Time course of motor gains induced by Music-supported Therapy after stroke: an exploratory case study¹

6.1 Introduction

Motor deficits are the most common outcome after a stroke and can include weakness, spasticity, slowness, or tremor (Pomeroy et al., 2011). Around 75% of stroke patients present paresis of the contralateral upper extremity (Rathore et al., 2002) that can affect coordination, precision, and dexterity, limiting the performance of activities of daily living (Langhorne et al., 2011). Overall, motor deficits have a fundamental impact on the lives of stroke patients, restricting their participation in various family, work, and leisure contexts and markedly reducing their quality of life (Visser et al., 2015).

The rehabilitation of motor deficits aims to facilitate plastic changes in the brain to restore lost functions (Cramer et al., 2011) through the use of tasks involving massed practice (Carmichael & Krakauer, 2013), shaping, modelling and feedback to promote skill learning (Krakauer, 2006). In this context, it is important that the tasks used in the rehabilitation process motivate the patients, having real-world relevance (Timmermans, Spooren, Kingma, & Seelen, 2010). In this regard, music has emerged as a very promising tool in neurorehabilitation since musical activities place unique demands on the nervous system (Zatorre et al., 2007) and can be adapted to utilise many basic principles of neurorehabilitation.

Music-Supported Therapy was developed for stroke patients by Schneider and colleagues (2007) with the aim of enhancing the hemiparesis of the upper extremity through playing music (Schneider, Schönle, Altenmüller, & Münte, 2007). Recent studies in both acute and chronic stroke patients have shown that Music-supported Therapy can improve upper extremity motor deficits, including gains in dexterity and movement kinematics (Altenmüller, Marco-Pallares, Münte, & Schneider, 2009; Rojo et al., 2011). Music-supported Therapy is aimed at promoting

¹ The results presented in this chapter correspond to:

Grau-Sánchez, J., Ramos, N., Duarte, E., Särkämö, T., & Rodríguez-Fornells, A. (2017). Time course of motor gains induced by music-supported therapy after stroke: An exploratory case study. *Neuropsychology*, 31(6), 624.

neuroplastic changes similar to those occurring during and after normal motor skill learning and training. Learning to play an instrument promotes functional and structural changes in motor and sensory regions of the brain as seen in musicians as well as in nonmusician individuals receiving intensive musical training (Altenmüller & Schlaug, 2015; Schlaug, 2015). In chronic stroke patients, Ripollés and colleagues (2015) recently observed neuroplastic changes induced by Music-supported Therapy, showing a reduction of activation in contralesional motor cortical areas during a simple motor task, resulting in a motor activation pattern more similar to that of a normally functioning brain (Ripollés et al., 2014). Moreover, an increase in the excitability of the sensorimotor cortex as well as changes in the cortical motor representation have been reported in subacute and chronic stroke patients treated with Music-supported Therapy (Amengual et al., 2013; Grau-Sánchez et al., 2013).

One of the key features of Music-supported Therapy may be the role of the auditory feedback in the training, since music playing requires the interaction of auditory-motor networks. It has been widely observed that auditory-motor coactivation takes place not only during musical performance but also when listening to musical pieces or when playing a silent instrument (Bangert et al., 2006; Baumann, Koeneke, Meyer, Lutz, & Jäncke, 2005). To account for this effect, a feedforward and feedback model has been proposed where the internal motor representation and the auditory expectation might influence the final motor output and also evaluate the performance of online movements (Zatorre et al., 2007). This sensory-motor interplay seems to be disrupted in stroke patients (Rodríguez-Fornells et al., 2012); however, it has been found that the activity of the premotor cortex, supplementary motor area, and precentral gyrus increases when stroke patients treated with Music-supported Therapy listen to the trained melodies. In addition, functional connectivity analysis has revealed that this coactivation of auditory and motor regions could be re-established in chronic stroke patients after Music-supported Therapy (Ripollés et al., 2014). In these studies investigating the plastic changes associated with Music-supported Therapy (Amengual et al., 2013; Grau-Sánchez et al., 2013; Ripollés et al., 2015), a control patient group treated with a different therapy has not been assessed and therefore, it is not possible to establish a direct link between the implications of auditory-motor circuits in motor recovery. Further research is needed to elucidate the mechanisms of neural plasticity promoted by Music-supported Therapy.

An interesting find was that Music-supported Therapy can have a positive impact not only on the motor domain, but also on cognition, mood, and quality of life. In a recent study, chronic patients treated with Music-supported Therapy showed a cognitive improvement in attention, speed of processing, and rate of verbal learning (Ripollés et al., 2014). In addition, Music-supported Therapy was found to reduce negative affective symptoms and increase positive affect and

quality of life. Similarly, listening to music daily has been found to enhance the recovery of verbal memory and focused attention and prevent negative mood in acute stroke patients. These behavioural gains were linked functionally to enhanced neural efficiency of auditory encoding, as indexed by the mismatch negativity response, and structurally to increased grey matter volume in spared prefrontal and limbic regions (Särkämö et al., 2010; Särkämö et al., 2014). Overall, music has a remarkable ability to elicit positive emotions, motivate and engage patients with rehabilitation, and promote recovery and brain plasticity (Altenmüller & Schlaug, 2015).

However, some aspects of Music-supported Therapy still remain unclear. First, previous studies have only evaluated patients at the beginning and at the end of the treatment. The exact time course and the intersession progression of the different motor effects of Music-supported Therapy across treatment have not been systematically explored. Second, Music-supported Therapy protocols are usually applied for a period of three to four weeks, but the potential benefit of repeating or extending the training has not been studied. Consequently, taking into consideration the first and second points, an optimal dose-response has not been established. Third, it is unclear if the motor improvements in chronic stroke patients treated with Music-supported Therapy are maintained without continuous treatment over time. Finally, the degree to which the gains observed in playing-related motor skills transfer to other motor tasks and generalise to better activities of daily living functions is still largely undetermined.

In this study, we present a stroke patient case study with an ABAB design, which aimed to (i) explore the progression of the rehabilitation of the motor deficits throughout the sessions of a four-week Music-supported Therapy treatment, (ii) examine the effects of a second Music-supported Therapy treatment period in the motor and functional domain, (iii) study the retention of gains during an off-treatment period, and (iv) investigate the generalization of gains on activities of daily living. Our hypotheses were that (i) the enhancement of playing-related motor skills and general motor skills induced by the Music-supported Therapy would show a different temporal trajectory; (ii) the second Music-supported Therapy period would be important for enhancing functional gains; (iii) motor gains would be maintained over time and (iv) transfer or generalization to other motor task would occur at the end of the training.

6.2 Methodology

6.2.1 Participants

The patient was a 55-year-old right-handed male who suffered an ischaemic stroke 18 months before his enrollment in the study at the Department of Physical Medicine and Rehabilitation of the Hospitals del Mar i de l'Esperança, Barcelona, Spain. The stroke was located in the right anterior choroidal artery, causing lesions in the right internal capsule and thalamus, and was classified as a small vessel occlusion following the TOAST criteria (Adams et al., 1993). Figure 1 A shows a structural Magnetic Resonance Imaging (MRI) T1-image of the lesion. At the acute stage, the patient presented dysarthria, inferior left facial paresis, and hemiplegia in the left upper and lower extremities, with a score of 11 on the National Institutes of Health Stroke Scale (NIHSS) that assesses presence and severity of symptoms after stroke (Brott et al., 1989). After being in the stroke unit, the patient received 8 months of a standard neurorehabilitation program in an intensive rehabilitation outpatient facility and was discharged 10 months prior to his participation in the study. At the beginning of the study, the patient still presented a slight paresis of the left upper extremity (UE) and mild paresis in the lower left extremity, needing a walking stick (NIHSS score = 3) and affecting the ability of the patient to perform instrumental activities of daily living. In regard to his education and past occupations, the patient studied until the age of 19, completing a vocational training course in mechanics. He worked as a security guard for 28 years, but since the stroke, the patient has retired because of his medical condition. The patient had not received any formal music education or musical training and reported to listen to music daily through TV, radio, and his smartphone, and to dance once a week at home. The styles of music the patient enjoys are jazz, swing, pop, and reggae. The patient obtained normal values in music pleasure, with a total score of 68 out of 100 in the Barcelona Music Reward Questionnaire that assesses reward experiences associated with music (Mas-Herrero et al., 2013).

In addition, normative data for nonstandardized outcome measures were obtained from altogether 15 healthy right-handed and age-matched control subjects (see below).

6.2.2 Experimental design

A reversal design (ABAB, Smith, 2012) where no treatment was provided in the *A* periods and Music-supported Therapy was applied in the *B* periods with repeated assessment across each period was implemented in a chronic stroke patient. The study was comprised of four 4-week stages (16 weeks in total): an initial baseline period (Weeks 1-4), first Music-supported Therapy

treatment period (MST-1, Weeks 5-8), a withdrawal period (Weeks 9-12) and a second Music-supported Therapy treatment period (MST-2, Weeks 13-16). An extensive assessment of motor function (see below) was performed at the end of each week (from Week 1 to 16). In addition, a longitudinal follow-up evaluation was done 3 months after the end of MST-2 (Week 28). Figure 1B illustrates the design of the study. The study was approved by the clinical research ethics committee of Parc de Salut Mar, Barcelona, Spain, and the patient gave written informed consent.

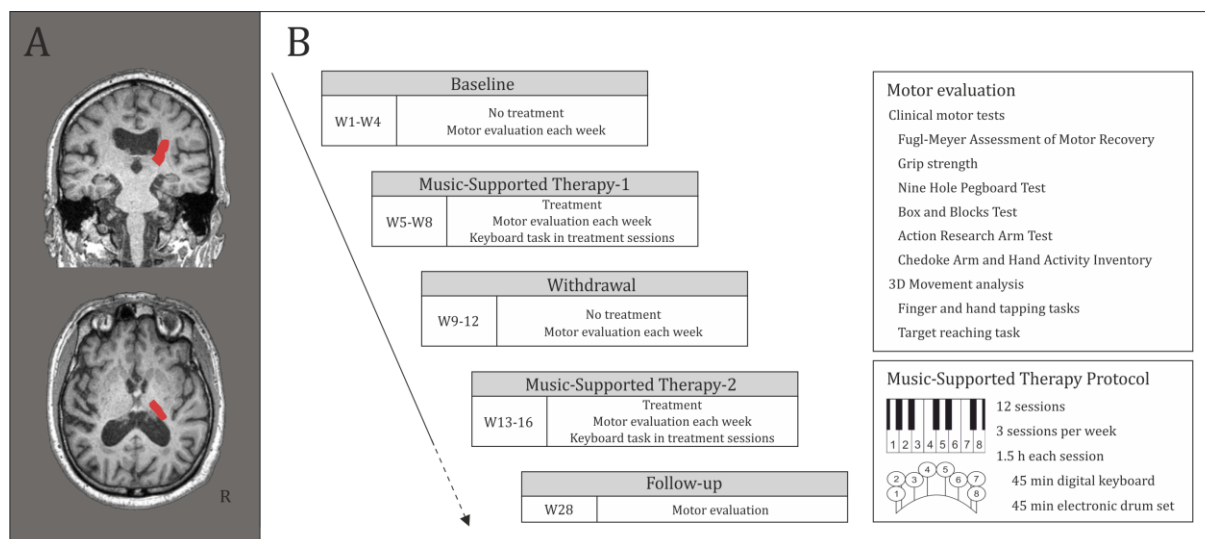


Figure 1. Location of participant's lesion and study design.

A) The lesion of the patient is shown in a magnetic resonance imaging (MRI) T1-image. The stroke was classified as a small vessel occlusion following the TOAST criteria and was located in the right anterior choroidal artery, causing lesions in the right internal capsule and thalamus. B) The study comprised four periods in an ABAB design: baseline, Music-supported Therapy-1 (MST-1), withdrawal, and Music-supported Therapy-2 (MST-2). A follow-up evaluation was performed 3 months after the last period. The weekly motor evaluation and the training protocol with Music-supported Therapy are described. W, week.

6.2.3 Music-Supported Therapy

The treatment periods (MST-1 and MST-2) both consisted of three Music-supported Therapy sessions of 1.5 h per week for four weeks (24 sessions, 36 hours in total). The central idea in Music-supported Therapy is to promote plastic changes in the sensorimotor cortex because of motor skill learning and facilitate the reestablishment of the audio-motor coupling loop (Rodríguez-Fornells et al., 2012). Patients play musical instruments with the UE, and importantly, the auditory feedback produced by the musical instrument may be used to evaluate online motor actions and to influence motor outputs.

In each session, a digital keyboard (CTK-810/WK110, Casio Europe GmbH, Norderstedt, Germany) and an electronic drum set of 8 pads (Roland drum system, TD-6KW, Roland Corporation, Hamamatsu, Japan) were used for 45 min each to train fine and gross movements

of the affected UE, respectively. The order in which each instrument was played was counterbalanced across sessions.

For the keyboard training, the instrument was on a table at a distance of ~35 cm from the edge. The patient was seated in front of the keyboard, with the elbow flexed at 90 and the forearm resting on the table. Only eight consecutive notes were used (C, D, E, F, G, A, B, C') and the hand was positioned in the middle of the octave with a slight extension of the wrist and the fingers resting on the keys. For the drum playing, the patient was seated in a chair without armrests, and the drum set was placed at a distance of ~45 cm with the 8 pads of 20 cm of diameter around both sides of the body. The pads produced piano sounds (C, D, E, F, G, A, B, C') to keep the auditory feedback constant during the session. The therapist was seated next to the patient or standing behind on the affected side, providing physical assistance when it was needed and correcting compensatory movements. The exercises consisted of playing simple tone sequences until the patient could learn to play short melodies following a modular regime. Exercises were first demonstrated by the therapist and then repeated by the patient. If the patient succeeded, the difficulty of the sequence was progressively increased. Stickers labelling the keys and the pads with numbers from 1 to 8 were used as a cue to produce sequences. The exercises with the keyboard involved movements of flexion, extension, adduction, and abduction of the fingers and thumb. The drum training, aimed to enhance gross motor function, required movements of flexion, adduction, and abduction of the shoulder as well as its internal and external rotation. Movements of flexion and extension of the elbow and wrist were needed to hit the pads. Overall, the training was aimed at increasing the range of movement, coordination, and speed.

6.2.4 Motor function assessment

An extensive evaluation of the motor function was performed at the end of each week using standardised motor tests and three-dimensional (3D) movement analysis. In addition, during the treatment periods, the performance of the patient playing an octave with the keyboard was recorded at the end of each session.

Clinical motor tests. To evaluate the level of impairment, the Upper Extremity subtest from the Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA, Fugl-Meyer et al., 1975) was administered. Grip strength of both UEs was measured with a dynamometer (E-Link System H500, Biometrics Ltd., Newport, United Kingdom) as the mean of three trials. Finger dexterity and gross manual dexterity were assessed with the Nine Hole Pegboard Test (9HPT, Parker et al., 1986) and the Box and Blocks Test (BBT, Mathiowetz et al., 1985), respectively. The unaffected (right) upper extremity was also evaluated with these two tests to compare the performance to

the affected (left) UE. The overall functioning of the affected upper extremity was evaluated with the Action Research Arm Test (ARAT, Lyle, 1981). The FMA, grip strength, 9HPT, BBT and ARAT were performed each week (Weeks 1-16).

The Chedoke Arm and Hand Activity Inventory (CAHAI, Barreca, Stratford, Lambert, Masters, & Streiner, 2005), which measures the ability of the affected upper extremity to perform bimanual tasks from activities of daily life, was only administered at the beginning of the study and at the end of each period (Weeks 1, 4, 8, 12, and 16). All the tests were also performed at the longitudinal follow-up evaluation (Week 28).

3D movement analysis. Movement analysis was performed using an ultrasonic device (CMS 50, Zebris, Isny, Germany) that recorded the continuous 3D spatial position of markers attached to the hand of the patient. Three different motor tasks were recorded with both UEs: a finger and a hand tapping task, and a target reaching task (Amengual et al., 2013). A control group of 10 healthy participants (all men, mean age 55.9 ± 6.4) performed the same evaluation at the beginning of the study.

For the finger and hand tapping task, participants were asked to perform a continuous tapping with the index finger or the whole hand, respectively. Three trials were recorded, and the following parameters were obtained per trial: (i) frequency, as the number of tappings per second, as well as, (ii) mean velocity, and (iii) smoothness of movement, as the number of inversions in the velocity per movement segment. The mean of the three trials was accounted for the analysis.

In the target reaching task, participants had to reach a round target of 0.8 cm in diameter that was placed on a table at a distance of 35 cm from the patient and at a height of 10 cm. Eight trials were recorded, and the mean of the trials was performed to obtain (i) the time to peak velocity in reaching, (ii) the maximum acceleration in reaching, and (iii) the smoothness of movement around the target.

Keyboard performance. At the end of each Music-supported Therapy session the patient was asked to play an octave (C, D, E, F, G, A, B, C') with the keyboard. This exercise was recorded for both the index and the middle finger, and the MIDI output was obtained. The same task was recorded at baseline for five healthy control participants (3 women, mean age 55.2 ± 3.4). The duration of the sequence was calculated as well as the strength used to strike the keys. As the strength was obtained for each individual key press, the mean of the 16 values of the octave (8 with the index finger and 8 with the middle finger) was calculated to have a score per sequence and session.

6.2.5 Data analysis

For the clinical standardised motor tests (with the exception of the CAHAI), we obtained 16 data points (4 per period) and calculated the mean of each period. The Minimal Detectable Change (MDC) or the Minimal Clinically Important Difference (MCID) of each test was added to the mean baseline to determine if the subsequent evaluations reached a clinically significant level of gain. The MDC estimates statistically the smallest change in an outcome measure that can be detected beyond the measurement error and represents a noticeable change in ability and similarly, the MCID is the smallest amount of change that is considered important by the patient or clinician.

Because of the high sensitivity of the 3D movement analysis parameters, the mean of each period was computed and compared with the mean of the control group. For the keyboard performance, the mean of the index and middle finger sequences was calculated per session and compared with the performance of the control participants.

6.3 Results

6.3.1 Clinical motor tests

The scores of the patient in all clinical motor tests at different time points are shown in Table 1. Figure 2 illustrates the results of those tests which showed a treatment effect.

Grip strength. The MCID for the grip strength of the affected (nondominant) upper extremity is 6.2 Kg (Lang, Edwards, Birkenmeier, & Dromerick, 2008). For the affected UE, the patient scored 29.7 (\pm 1.5) Kg at baseline Figure 2A. During MST-1 and MST-2, the mean grip strength increased progressively to 33.4 (\pm 1.5) Kg and 34.7 (\pm 1.6) Kg, respectively, but did not quite reach the MCID level (only the second week of MST-2 showed a significant improvement above MCID). An interesting find was that during the withdrawal period, the mean score returned to the baseline levels (29.5 \pm 2.1 Kg), indicating that MST-1 was not enough to achieve lasting gains. In contrast, at the longitudinal follow-up (Week 28), the grip strength remained at a similar level as in MST-2. For the unaffected UE, the baseline mean grip strength of the patient (44.5 Kg \pm 1.6 Kg) was already within normal limits for his age (45 Kg) (Massy-Westropp, Gill, Taylor, Bohannon, & Hill, 2011) and remained relatively similar during the follow-up.

BBT. In the BBT, the mean score of the patient for the affected upper extremity at baseline was 31.2 (\pm 2.3) blocks per minute, and the MDC is 5.5 blocks per minute (Chen, Chen, Hsueh, Huang, & Hsieh, 2009) (Figure 2B). Therefore, a score above 36.7 was considered as clinically relevant. During MST-1, there was a slight mean increase to 34.5 (\pm 2.5) blocks per minute, exceeding the

MDC on the last week (38 blocks per minute). At the withdrawal phase, the patient remained stable in this test, maintaining the gains, with a mean score of 37.2 (\pm 0.9). During MST-2, the patient continued improving, and the mean performance was clearly above the MCD (40.5 \pm 2.3). More important, this significant gain was maintained in the follow-up evaluation at Week 28 (39 blocks per minute). Interestingly, the unaffected upper extremity exhibited a similar pattern, with progressive improvement toward the end of MST-1, plateauing at withdrawal, and further improvement during MST-2, indicating a positive transfer effect of the Music-supported Therapy for gross motor speed of the unaffected UE.

ARAT. In the ARAT test, the patient had a relatively high mean score already at baseline (52 \pm 1.4). However, during the MST-1, withdrawal, and MST-2 periods, the patient showed progressive gains in the mean score, which reached MCID (5.7 points above baseline (van der Lee, Beckerman, Lankhorst, & Bouter, 2001) at MST-2 (Figure 2C). In the follow-up evaluation (Week 28), the improvements seen during the MST-2 were, however, not maintained.

CAHAI. The CAHAI was administered only at the beginning and at the end of each period. The results of this test are presented in Figure 2D. For the baseline period, we calculated the mean, which was 70.5 (\pm 3.5). The MDC is 6.3 points (Barreca et al., 2005), which was achieved already after MST-1 (79 points). This relevant level of gain was stable over the withdrawal period and, importantly, the patient still continued improving during MST-2 (80 points). At the follow-up evaluation, the gains were also maintained.

FMA and 9HPT. For the FMA and 9HPT (Wagner, Rhodes, & Patten, 2008; Chen et al., 2009), the MDC was not achieved in any of the evaluations although the patient progressively obtained better scores in the 9HPT during the treatment periods.

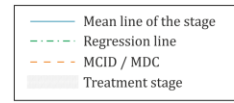
In summary, these results indicated that major clinical motor gains were noticeable at the end of MST-1 and during MST-2.

Table 1. Results of the clinical motor tests.

	FMA*	Grip strength		9HPT*		BBT*		ARAT*	CAHAI*
		Aff	Unaff	Aff	Unaff	Aff	Unaff		
Baseline									
W1	62	28.7	45.6	40	27	33	49	52	73
W2	58	30.6	45.7	47	23	31	46	54	
W3	62	31.4	42.2	45	26	33	48	51	
W4	60	28.1	44.5	50	27	28	45	51	68
Mean	60.5	29.7	44.5	45.5	25.7	31.2	47	52	70.5
SD	1.9	1.5	1.6	4.2	1.8	2.3	1.8	1.4	3.5
MCID/MDC	65.7	35.9	50.7	19.8	18.9	36.7	52.5	57	76.8
MST-1									
W5	62	33.5	47.6	44	23	32	45	51	
W6	63	34.9	50.3	41	22	34	46	55	
W7	64	34.2	48.6	38	24	34	49	53	
W8	63	31.3	43.5	39	23	38	54	55	79
Mean	63	33.4	47.5	40.5	23	34.5	48.5	53.5	
SD	0.8	1.5	2.8	2.6	0.8	2.5	4	1.9	
Withdrawal									
W9	62	32.6	45.3	41	21	37	56	52	
W10	62	27.9	45.2	41	24	38	55	56	
W11	61	29.6	47.5	39	24	38	57	57	
W12	62	28	43.1	41	22	36	56	56	78
Mean	61.7	29.5	45.2	40.5	22.7	37.2	56	55.2	
SD	0.5	2.1	1.8	1	1.5	0.9	0.8	2.2	
MST-2									
W13	63	33.3	45.8	38	23	41	62	57	
W14	62	36.7	45.5	35	19	42	60	56	
W15	62	33.4	48.9	37	23	37	56	56	
W16	63	35.4	49.5	39	22	42	64	57	82
Mean	62.5	34.7	47.4	37.2	21.7	40.5	60.5	56.5	
SD	0.5	1.6	2	1.7	1.8	2.3	3.4	0.5	
Follow-up									
W28	64	32.4	47.8	46	20	39	59	55	80

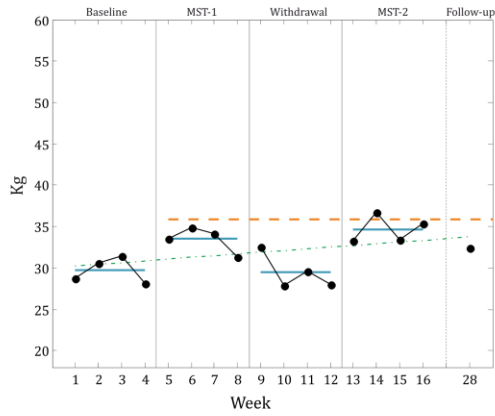
The results for the clinical motor test are presented by each upper extremity (affected, unaffected), period (baseline, MST-1, withdrawal, and MST-2), and evaluation (weeks from 1 to 16 and follow-up at Week 28). The mean and the SD are calculated by period. The minimal detectable change (MDC) or minimal clinically important difference (MCID) of each test was added to the mean baseline. W, week; FMA, Fugl-Meyer Assessment of Motor Recovery after Stroke; 9HPT, Nine Hole Pegboard Test; BBT, Box and Blocks Test; ARAT, Action Research Arm Test; CAHAI, Chedoke Arm and Hand Activity Inventory. The maximum score for the FMA is 66. The grip strength is expressed in kilograms. The 9HPT is reported as the seconds needed by the patient to perform the task. For this test, it is not possible to subtract the MDC (32.8 s) from the baseline as the score does not make sense for the task. Instead, the normative values are presented. The BBT accounts the number of cubes that the patient is able to pass from one box to another in 1 minute. The maximum score of the ARAT is 57 and 91 for the CAHAI.

Clinical motor tests

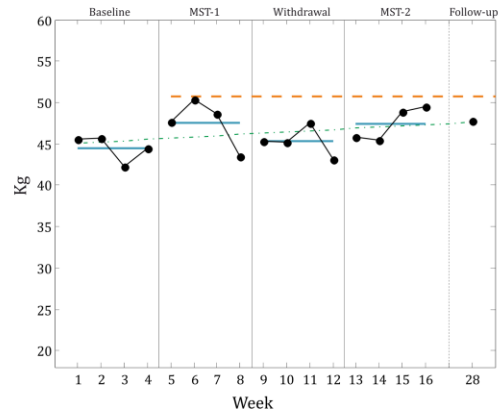


A. Grip Strength

Affected Upper Extremity

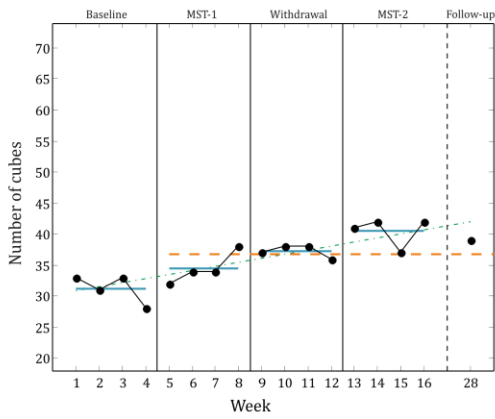


Unaffected Upper Extremity

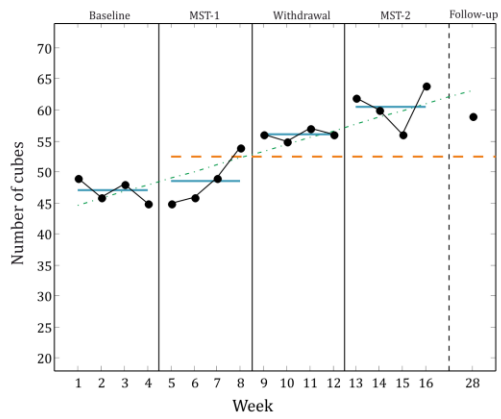


B. Box and Blocks Test

Affected Upper Extremity

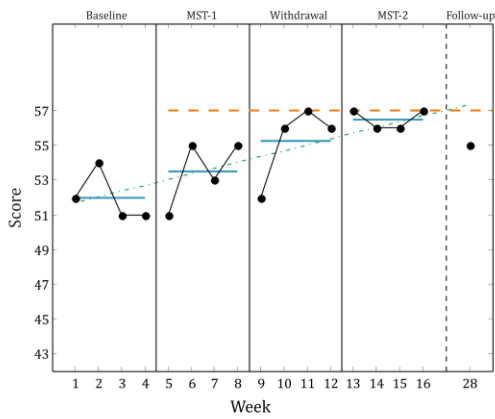


Unaffected Upper Extremity



C. Action Research Arm Test

Affected Upper Extremity



D. Chedoke Arm and Hand Activity Inventory

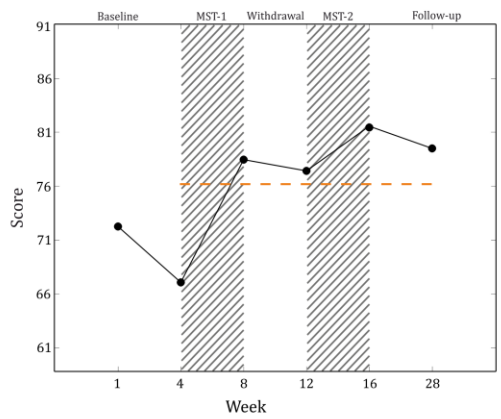


Figure 2. Results of the clinical motor tests.

The most relevant findings regarding the clinical evaluation are shown. The score obtained by the patient at each evaluation is displayed (weeks from 1 to 16 and Week 28). In each period, the mean of the participant was calculated (green line) and the Minimal Detectable Change (MDC) or Minimal Clinically Important Difference (MCID) was added to the mean baseline (orange line). A regression line considering all the data points was performed to explore the tendency of the outcome across the different evaluations (blue line). A) Results of the grip strength for both extremities expressed in kilograms. B) Results of the Box and Blocks Test. The number of cubes that the patient is able to pass from one box to another in 1 minute is presented for both extremities. C) Results of the Action Research Arm Test, which has a maximum punctuation of 57. D) Results of the Chedoke Arm and Hand Activity Inventory. This test was performed only during Weeks 1, 4, 8, 12, 16, and 28. The maximum punctuation is 91. See the online article for the color version of this figure.

6.3.2 3D movement analysis

Table 2 shows the scores for the 3D movement analysis where the mean of each period was calculated. The mean velocity of the affected upper extremity in both finger and hand tapping tasks improved during both MST-1 and MST-2, even rising above the mean score of the controls for the hand tapping task (701.6 ± 65.5 mm/s) (Figure 3A and B). For the unaffected UE, the mean velocity of the hand tapping increased during both MST-1 and MST-2 while the mean velocity of the finger tapping showed some increase only during MST-2. The smoothness of the finger tapping for both UEs was comparable with the controls across the follow-up, showing no clear changes. In the hand tapping task, the smoothness of the affected upper extremity also remained relatively stable during MST-1 and MST-2, but showed a decline in the withdrawal period. The frequency of both finger and hand tapping tasks for both UEs was smaller than the frequency that controls exhibited and did not show any improvement over time.

Table 2. Results of the three-dimensional (3D) movement analysis.

3D movement analysis measure	Baseline	MST-1	Withdrawal	MST-2	Follow-up	Controls
Finger tapping						
Frequency Affected	1.5 (0.1)	2 (0)	1.8 (0.2)	2.1 (0.1)	1.8	4.3 (1.7)
Frequency Unaffected	2.8 (0.8)	2.1 (0.3)	1.8 (0.1)	2.2 (0.2)	2	4.4 (1)
Mean Velocity Affected	138.5 (16.1)	155.1 (16.3)	164.1 (17.5)	191.1 (16.2)	181	222.6 (67.7)
Mean Velocity Unaffected	189.8 (39)	190.7 (21.3)	188.2 (8.9)	217.8 (15.1)	232.5	195.3 (63.6)
Smoothness Affected	1 (0)	1 (0)	1 (0)	1 (0)	1	1 (0)
Smoothness Unaffected	1 (0)	1.1 (0.1)	1 (0)	1 (0)	1	1 (0)
Hand tapping						
Frequency Affected	1.6 (0.1)	1.8 (0.1)	1.9 (0.1)	2 (0.1)	2	3.7 (1.3)
Frequency Unaffected	1.8 (0.1)	2 (0.1)	1.8 (0)	2.1 (0.2)	2	3.9 (1.7)
Mean Velocity Affected	395.2 (73.3)	552.8 (73.6)	620.9 (50.2)	701.6 (65.5)	640	529 (229.3)
Mean Velocity Unaffected	458.2 (61.1)	722.5 (92.2)	693.1 (59.8)	810.5 (92.3)	753.5	418.3 (149.4)
Smoothness Affected	1 (0)	1.1 (0.1)	1.4 (0.1)	1.1 (0)	1.3	1 (0.1)
Smoothness Unaffected	1 (0)	1 (0.1)	1 (0)	1.1 (0.1)	1	1 (0)
Target reaching						
Time to peak velocity Affected	190 (36.1)	201.4 (31.3)	182.4 (32.8)	144.4 (19.6)	121.6	148.6 (41.4)
Time to peak velocity Unaffected	224.2 (14.5)	216.6 (35.9)	224.2 (14.5)	186.2 (63.7)	243.2	156.5 (35.8)
Maximum Acceleration Affected	58.4 (27.9)	52.4 (18.5)	59.1 (7.5)	65.5 (19.2)	75.2	70.3 (33.4)
Maximum Acceleration Unaffected	40 (10.8)	51.1 (6.9)	61.9 (5.9)	55 (11.1)	39.5	61.9 (30.3)
Smoothness Affected	5 (2.8)	4.7 (0.5)	2.2 (0.9)	2 (1.4)	4	3.2 (1.6)
Smoothness Unaffected	3 (0)	3 (0.8)	2 (0)	2.2 (0.5)	2	2.7 (1.2)

The mean and the SD for the finger and hand tapping, and reaching tasks are presented by each upper extremity (affected, unaffected) and period (baseline, MST- 1, withdrawal, and MST-2). The results of the follow-up evaluation are also shown. The mean and SD of controls at baseline is also presented. The frequency is expressed in Hertz, the mean velocity in millimeters per square, the time to peak velocity in milliseconds, and the maximum acceleration in millimeters per square seconds. The smoothness is the number of velocity inversions per movement segment and typically is expected to be 1.

In the target reaching task (Figure 3C), the patient's performance with the affected upper extremity became faster especially during MST-2, as indicated by decreased time to achieve a maximum velocity of movement (144.4 ± 19.6 ms). The time-to-peak velocity of the unaffected upper extremity was not within the normal range of controls at any time point. Although the

maximum acceleration scores for both UEs were within normal range scores, there was a slight increase in MST-2 ($65.5 \pm 19.2 \text{ mm/s}^2$) for affected UE. The smoothness of the movements when approaching the target improved during the withdrawal and MST-2 periods, reaching scores that were below the mean of controls for both UEs.

In summary, the results from the 3D movement analysis indicated that during the treatment periods the velocity in the finger and hand tapping task improved. In contrast, the parameters in the reaching task only improved during the second treatment period (MST-2).

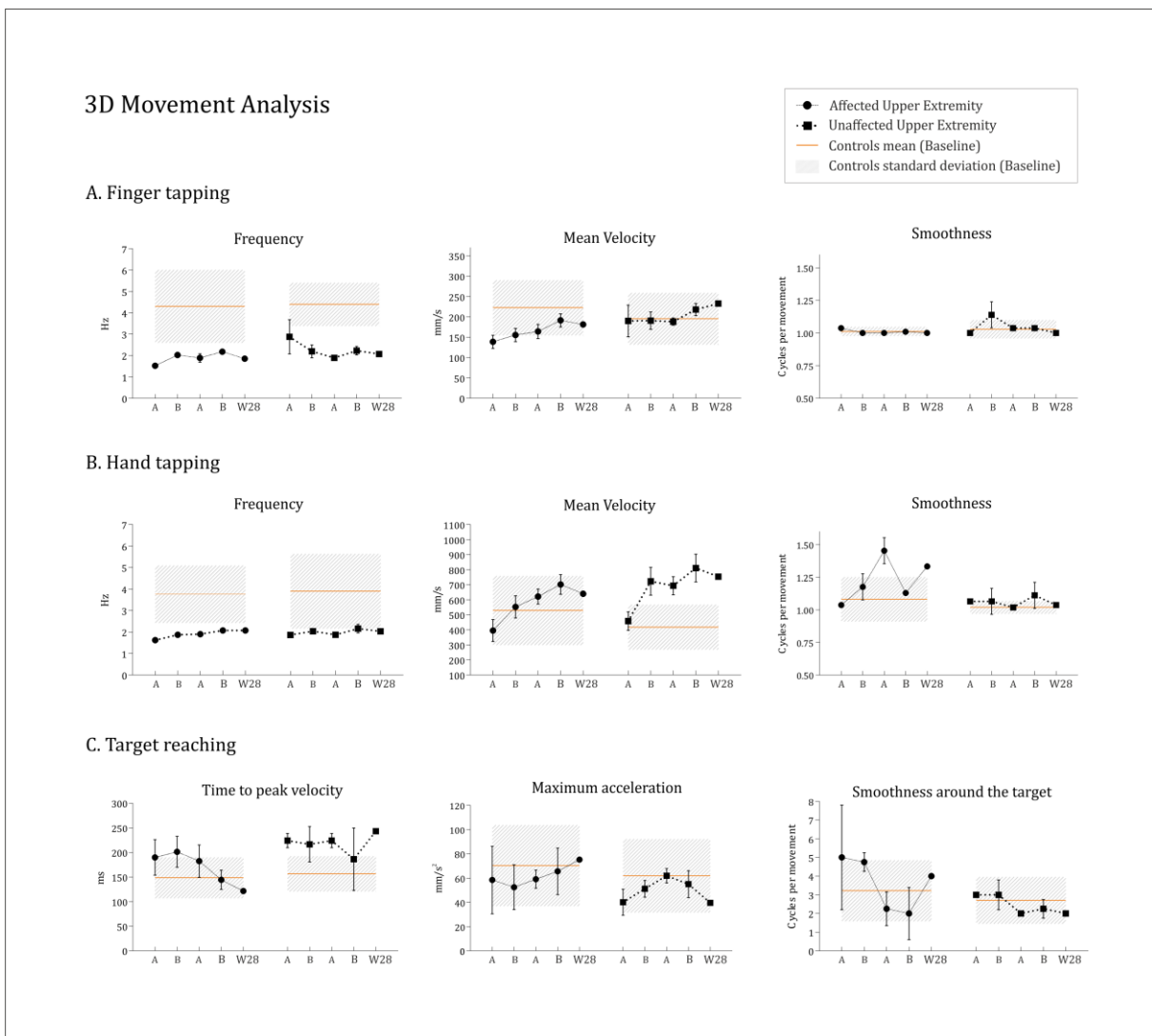


Figure 3. Results of the three-dimensional (3D) movement analysis.

The results of the finger and hand tapping, and a reaching task are displayed for both extremities and each period (A, baseline; B, Music-supported Therapy, MST-1; A, withdrawal; B, MST-2) and the follow-up evaluation (Week 28). The mean of the controls and the SD of their performance at baseline are presented. A) Results of the finger tapping task. B) Results of the hand tapping task. C) Results of the target reaching task. The frequency is expressed in Hertz, the mean velocity in millimeters per second (mm/s), the time to peak velocity in milliseconds (ms), and the maximum acceleration in millimeters per square second (mm/s²). The smoothness is the number of velocity inversions per movement segment and typically is expected to be 1. See the online article for the color version of this figure.

6.3.3 Keyboard performance

The sequence duration, obtained as the mean of the two sequences (with the index and middle finger), decreased steadily across the sessions during MST-1 (Figure 4A). During MST-2, the gains in this parameter were maintained, but no further progress was observed. Also, the variance of performance within each session decreased toward the end of MST-1 and remained smaller during MST-2. However, the performance of the patient remained slower than that of the controls.

A similar pattern of results was observed for the amount of pressure applied when pressing the keys of the keyboard. During the first half of MST-1, key pressure was smaller and also more variable than in controls (Figure 4B). However, from session eight of MST-1, the performance of the patient started to show more power and stability, reaching normal range compared with controls. These gains were again maintained during MST-2.

In summary, the results from the analysis of keyboard performance indicated that the main gains in terms of speed and strength were seen during MST-1.

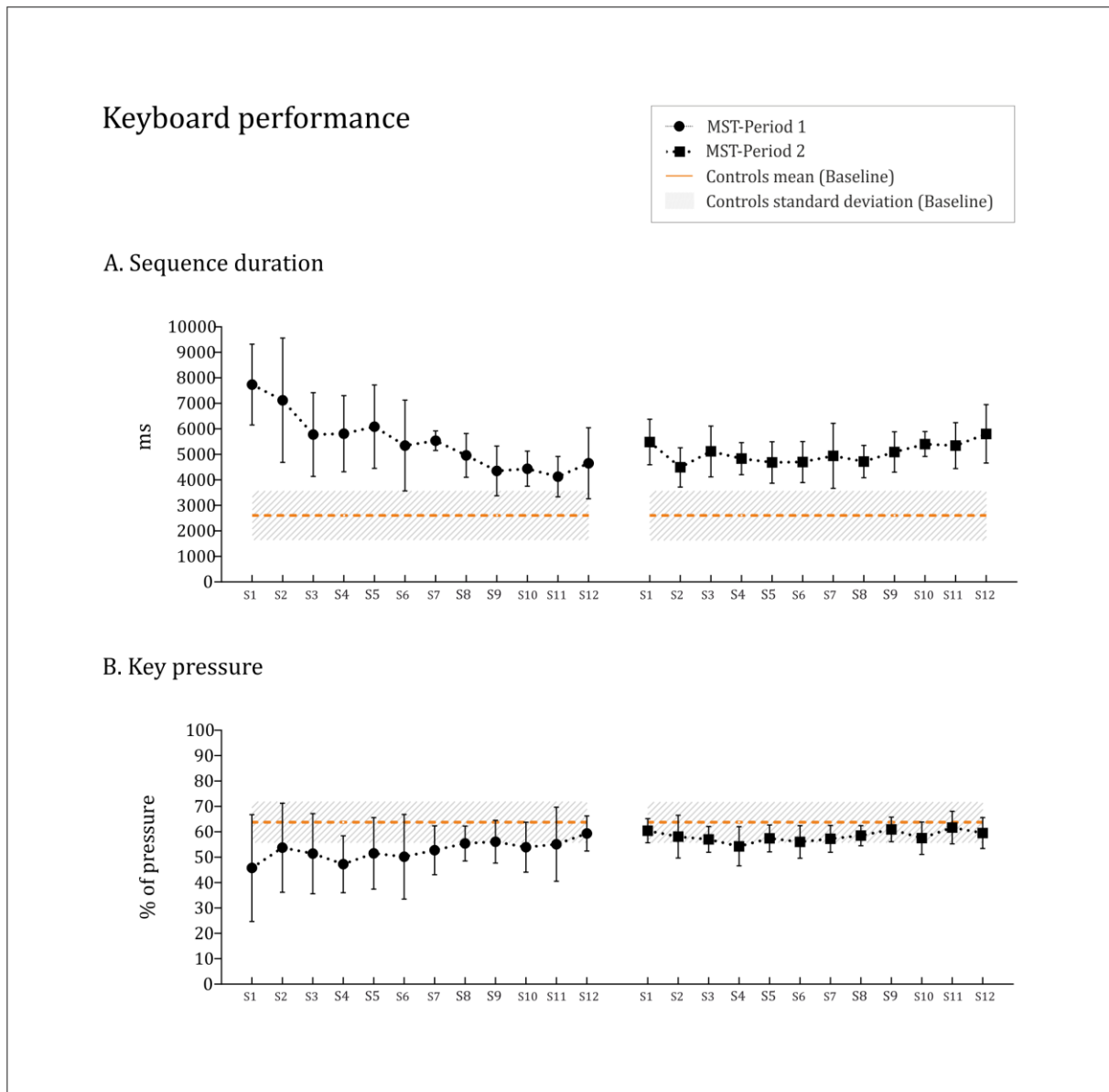


Figure 4. Results of the keyboard performance.

The performance of playing an octave is shown across sessions for both treatment periods (Music-supported Therapy, MST-1 and MST-2). The mean and SD of the controls' performance at baseline are presented. A) Results of the sequence duration. The duration of playing an octave is presented in milliseconds. B) The key pressure with the patient strike the keys is displayed. See the online article for the color version of this figure.

6.4 Discussion

This study examined the progression of the motor and functional gains of a chronic stroke patient treated with Music-supported Therapy in a case study with an ABAB design. Three different types of evaluation were performed: (i) the clinical motor test assessed the functional use of the hand in other tasks not directly related to the treatment and in activities of daily living, (ii) the 3D movement analysis evaluated the kinematic properties of movements, and (iii) the keyboard task assessed the motor performance in a task specific to the training.

The patient showed significant improvements in the clinical motor domain at the end of MST-1 (BBT and CAHAI), and during MST-2 (grip strength, BBT, ARAT, and CAHAI). Some of these gains were maintained over time as shown in the follow-up evaluation performed 3 months after MST-2. Moreover, the velocity of a finger and hand tapping task increased during MST-1 and MST-2, whereas the kinematic properties of a reaching task improved only in MST-2. Importantly, gains in a keyboard task were only seen during the first sessions of MST-1. These results are in line with previous research validating Music-supported Therapy in subacute and chronic stroke patients where motor improvements were also observed. For instance, similar results in the BBT and ARAT scores have been reported in stroke patients who received Music-supported Therapy (Grau-Sánchez et al., 2013; Ripollés et al., 2014). In addition, improvements in a finger and hand tapping task have also been found after the application of Music-supported Therapy (Amengual et al., 2013; Schneider et al., 2007).

MST is a task-specific training, aimed to elicit similar processes as those occurring during and after motor skill learning, where movements become more accurate and faster with practice (Dayan & Cohen, 2011). It is known that the acquisition of a new motor skill develops quickly at the beginning of training (Censor, Sagi, & Cohen, 2012). In this sense, major improvements were seen during the first sessions of MST-1 in the keyboard task. The patient pressed the keys with more strength and needed less time to play an octave. Similarly, the finger and hand tapping velocity increased during MST-1. Importantly, these movements are required for the keyboard and drum pads playing. Therefore, both the keyboard task and the finger and hand tapping tasks evidenced fast acquisition and task-specific learning. Only at the end of MST-1 improvements were observed at a functional level as the patient obtained significantly better scores in the BBT and CAHAI. The patient also improved during MST-1 as observed in other tests such as the grip strength, the ARAT and the 9HPT although these gains were not significant.

In the withdrawal period, this patient did not receive any kind of treatment, which can be compared to an offline period in the process of motor skill learning (Dayan & Cohen, 2011). It has been reported that in the absence of practice there is stabilisation and consolidation of motor memory traces, where new motor memories could become more robust (Robertson, Pascual-Leone, & Miall, 2004). During this period, the scores for the BBT and CAHAI remained stable. The fact that these gains were maintained over time may evidence long-term retention. It has been discussed that improvements can take place also during offline periods (Censor et al., 2012). This was the case for the ARAT evaluation, where the patient improved slightly during the withdrawal period. However, the gains observed in the grip strength disappeared.

The additional treatment provided during MST-2 may be considered as a period where memory reactivation of motor traces occurs, and it is further modified with practice. In this period, the patient did not show any improvement in the keyboard task. The key pressure remained at the same level that the patient reached in MST-1, being within the normative values of controls. The duration of the octave also remained as in MST-1 although did not reach similar times compared with controls. On the other hand, the patient reached a significant level of gain in the BBT in and CAHAI during MST-2, and in some of the evaluations of this period in the ARAT and grip strength. Besides, the mean velocity of the finger and hand tapping tasks as well as the time-to-peak velocity, maximum acceleration and smoothness of the reaching task improved during MST-2. Overall, major gains in the clinical motor tests were seen in MST-2, meaning that generalisation to other tasks occurred mostly during this period. Most of the clinical motor gains were maintained in the follow-up evaluation, which may reflect improved long-term retention.

With regard to the aims of the study, the interim conclusions are that (i) fast acquisition within the same task occurs during the first Music-supported Therapy sessions, but generalization to other motor tasks is prominent only at the end of the Music-supported Therapy training; (ii) the second Music-supported Therapy training does not have effects on the musical instrument performance but it may be important for the generalization of improvements to other tasks and long-term retention; (iii) during the withdrawal period gains can be maintained, improved or lost; and (iv) generalization of gains to activities of daily living occurs during the second treatment period.

Indeed, one of the important findings of the present study is the improvement seen in the CAHAI. This test evaluates the functional ability of the affected upper extremity in performing bimanual tasks from activities of daily living. For instance, the patient is asked to make a phone call, pour a glass of water, or put toothpaste on a toothbrush, among other tasks. Previous literature on Music-supported Therapy had never evaluated this domain, and importantly, this study points out that the motor improvements because of Music-supported Therapy may be transferred to activities of daily living. This may be crucial as the ultimate goal in stroke motor rehabilitation is to reduce the limitations in activities of daily living, which have an impact on the participation and the quality of life of patients (Langhorne et al., 2011).

The FMA and the 9HPT were the only clinical motor tests that did not show any significant improvement in any of the evaluations. For the 9HPT, the patient progressively scored less across the different evaluations, but the change was not significant. The MDC for this test, which is 32, was established in a sample of acute stroke patients who usually present major room for improvement (Turton & Pomeroy, 2002). One possible explanation for the lack of results in this

test may be that the MDC is difficult to achieve in chronic stroke patients. Moreover, previous studies in chronic stroke patients treated with Music-supported Therapy did not find any improvement in this test (Amengual et al., 2013; Grau-Sánchez et al., 2013; Ripollés et al., 2014). Thus, it could be argued that Music-supported Therapy does not promote gains that can be observed with this test in chronic stroke patients.

With respect to the training protocol, the study from Schneider and colleagues (2007) had 15 sessions whereas the studies in chronic patients contained 20 sessions (Rodríguez-Fornells et al., 2012; Schneider et al., 2007). In these studies, the sessions were administered daily for 30 minutes. In contrast, in the present study, the patient received only three sessions per week which made the training more distributed with longer rest periods between sessions. Moreover, the sessions lasted 1.5 h and thus, were more intense. This modification was intended to facilitate a major degree of improvement as this depends on the amount of practice (Lage et al., 2015). In addition, two instruments were used in each session, where the first half of the session was dedicated to playing one instrument and the last part to playing the other one. This contextual interference is thought to be positive for the training as it has been described that better performance is achieved if more than a single task is practised alone (Krakauer, 2006; Pauwels, Swinnen, & Beets, 2014). A future modification of the protocol could be to involve both extremities in the activity where the unaffected upper extremity can serve as an intrasubject control. Bilateral arm training has emerged in the past years based on the idea that the majority of everyday tasks and activities require the use of both extremities and that rehabilitation programs with more ecological approaches may be more effective in improving the autonomy of patients (McCombe Waller & Whittall, 2008). Different studies have demonstrated the effectiveness of bilateral training with sensory feedback (Stewart, Cauraugh, & Summers, 2006) and specifically with rhythmic auditory cueing (Whittall, Waller, Silver, & Macko, 2000). Future studies should investigate the effectiveness of applying Music-supported Therapy as bilateral arm training.

As mentioned, Music-supported Therapy has been already evaluated in previous studies using experimental designs where two groups are compared at pre and post intervention (Altenmüller et al., 2009; Amengual et al., 2013; Ripollés et al., 2015; Rodríguez-Fornells et al., 2012). Given the existing evidence about its benefits, the aim of the present study was to explore the progression of motor recovery in Music-supported Therapy using single-case methodology. This type of methodology, which is frequently used in psychology, rehabilitation or education, is more sensitive to individual differences and the participant serves as his or her own control. However, single-case designs are subject to several limitations, such as order effects or blinding of the patient and therapist, which is difficult in behavioural interventions. In the case of stroke

rehabilitation, we dealt with irreversibility and carry-over effects, not having a clear reversion in the withdrawal for most measures. However, this is in favour of the intervention tested, since improvements are maintained over time and do not disappear when the treatment is concluded. Although previous studies have included both haemorrhagic and ischaemic stroke patients in their samples, the description of the pattern of progression of this study is from a patient with an ischaemic stroke. Future research should investigate whether haemorrhagic stroke patients treated with Music-supported Therapy show a similar time course of motor gains.

In summary, this study evaluated the progression of the motor and functional improvements in a chronic stroke patient treated with Music-supported Therapy. Given the exploratory nature of the study, its results cannot be generalised but may provide a deeper understanding of the motor progression in Music-supported Therapy and raise new questions with regard to the Music-supported Therapy protocol. Future studies are needed to further investigate how these variations in the Music-supported Therapy protocol as well as the offline periods benefit the recovery of motor deficits.

General discussion

Chapter 7. General discussion

Hemiparesis of the upper extremity is prevalent in the majority of stroke patients, affecting individuals' autonomy and their quality of life (Mayo et al., 2002; Rathore et al., 2002). In the absence of more effective procedures and pharmacological treatments to save neural tissue, the recovery of motor deficits relies almost exclusively on rehabilitation (Langhorne et al., 2011). Stroke rehabilitation aims at improving and maintaining patient's functioning at many different levels through restitution, substitution and compensation of functions.

There are several techniques to rehabilitate the motor function of the upper extremity after stroke (Winstein et al., 2016). Currently, music-based interventions have emerged as a promising tool in stroke motor rehabilitation because they can be applied as a form of training and multimodal stimulation (François et al., 2015). Specifically, Music-supported Therapy has been developed to treat the hemiparesis of the upper extremity in stroke patients by playing musical instruments (Schneider et al., 2007).

This thesis aimed at testing the effectiveness of Music-supported Therapy in the rehabilitation of upper extremity motor function after stroke. The present work was composed of four studies that used different research designs that may contribute to a better understanding of Music-supported Therapy.

In **Study 1**, we tested the effectiveness of Music-supported Therapy in enhancing the motor function, inducing neuroplastic changes in the sensorimotor cortex and improving the quality of life in subacute stroke patients (< 6 months from the stroke). Using an interventional experimental design, we found that patients enhanced their motor function after a four-week program of Music-supported Therapy. This motor improvement was accompanied by changes in the excitability of the sensorimotor cortex and a shift in the cortical motor map. Moreover, the patients' quality of life also improved after the treatment.

In **Study 2**, a RCT evaluated the effectiveness of adding Music-supported Therapy to a standard rehabilitation program for subacute stroke patients. Two groups were established to compare Music-supported Therapy to conventional therapy. Patients in both groups were also undergoing a standard program of rehabilitation. This study showed that both groups improved their motor function after the therapy and that these gains were maintained three months after finishing the treatment. Importantly, patients treated with Music-supported Therapy reported better language abilities in their daily lives when compared to patients who only received conventional therapy. Further analysis showed that patients in the Music-supported Therapy group increased their rate of verbal learning, reported less fatigue and negative emotions and

experienced a better quality of life after the treatment. Importantly, the motor gains were related to the individual's capacity to experience pleasure from musical activities in those patients treated with Music-supported Therapy.

In **Study 3**, a subsample of **Study 2** was evaluated before and after the intervention with structural and functional Magnetic Resonance Imaging to characterise the neural damage, study the relationship between corticospinal tract integrity and motor improvement, and explore neural plastic mechanisms induced by Music-supported Therapy compared to conventional treatment. We found that both groups of patients had lesions that were mainly located in subcortical structures and that there were no differences in the amount of damage to the main white matter frontal tracts. We did not find evidence on the relationship between the integrity of the corticospinal tract and motor recovery. Moreover, patients in the Music-supported Therapy group showed major activations of temporal regions of the affected hemisphere in a motor task after the therapy.

In **Study 4**, we used a single-case design to investigate the time course of motor improvements, the effects of providing a second period of training, the retention of motor gains over time, and the generalisation of gains to daily life activities in a chronic stroke patient treated with Music-supported Therapy. During the first period of training with Music-supported Therapy, movement kinematics and functionality of the upper extremity improved. However, the second period of treatment was necessary to obtain significant gains. The patient's performance in a musical task improved and reached a plateau within the first training sessions. The gains in motor function were maintained over time, and generalisation of motor improvements to daily life activities took place at the end of both periods of training.

In this chapter, I make an effort to integrate the results of these four studies by addressing the following aspects: the effects of Music-supported Therapy on motor function, cognition, mood and quality of life, the role of musical reward for the treatment success, and the mechanisms of brain plasticity induced by Music-supported Therapy. I follow by addressing the clinical implications of the results and how they can be integrated into the process of designing, testing and implementing a new treatment into clinical practice. Finally, I highlight the strengths and limitations of the present work and propose new perspectives for future studies.

7.1 Music-supported Therapy and its effects on the motor function

In the four studies contained within this thesis, we observed that the functionality of the upper extremity improved in stroke patients after Music-supported Therapy. However, little was

known as to whether Music-supported Therapy is better than other conventional rehabilitation approaches, if it promotes true recovery and which is the time course of motor gains.

7.1.1 Music-supported Therapy compared to conventional therapy

In **Study 1**, subacute patients improved their motor ability after the training with Music-supported Therapy. However, the lack of a control group of patients undergoing a different treatment was a limitation in order to clearly conclude that improvements were due to Music-supported Therapy. Two aspects acted as confounding variables in this study. Firstly, patients were enrolled in a standard rehabilitation program, meaning that they were receiving other types of therapy that could lead to the observed motor improvements. Secondly, patients were in the subacute stage. In this phase, spontaneous biological recovery is thought to contribute to improvements through endogenous plasticity mechanisms (Buma et al., 2013). Thus, we could not clarify that Music-supported Therapy specifically induced motor gains.

In **Study 2**, we used a different methodology, and the effect of adding Music-supported Therapy to the standard rehabilitation program for subacute stroke patients was compared to conventional treatment in an RCT. Importantly, we controlled the fact that patients were undergoing other types of therapy and the influence of spontaneous biological recovery since these two confounding aspects were present in the experimental and the control group. The only difference between groups was the extra training time with Music-supported Therapy or conventional therapy provided to participants. We found that adding Music-supported Therapy to a standard program of rehabilitation was not superior to conventional therapy approaches in the recovery of upper extremity function after stroke.

Two previous RCTs compared Music-supported Therapy to conventional treatment in subacute stroke patients, finding a superior effect in favour of Music-supported Therapy (Altenmüller et al., 2009; Schneider et al., 2007). In these studies, patients treated with Music-supported Therapy improved in the functional use of the affected extremity and movement kinematics significantly more than patients treated only with conventional therapy. The positive results of these two RCTs led us to hypothesise a larger effect of Music-supported Therapy than conventional therapy when conceptualising and designing **Study 2**. Having obtained a different result, we explored the possibility that the discrepancy between studies may be due to training intensity.

In the study of Schneider and colleagues (2007), patients in both the experimental and the control group received 13.5 hours of standard rehabilitation. In addition to that, the experimental group received 15 sessions (30 min each) of Music-supported Therapy, but no

more extra sessions were provided to the control group. Thus, patients in the Music-supported Therapy group trained 7.5 hours more than patients in the control group. This is a critical confounding aspect since it is unclear if improvements were due to Music-supported Therapy or to training intensity differences between groups. Similarly, Altenmüller and colleagues (2009) did not provide an extra time of therapy to the control group. In our study, both groups were enrolled in a standard rehabilitation program that consisted of 40 hours of conventional treatment for four weeks. This program was composed of two 1-hour daily sessions of physiotherapy and occupational therapy. Physiotherapy sessions focused on exercising global mobility whereas occupational therapy sessions aimed at regaining fine and gross mobility of the upper extremity through task-specific training. In these sessions, rehabilitative techniques that were used are evidence-based, which means that they have already been validated and accepted into clinical practice because of their effectiveness (Winstein et al., 2016). Apart from this standard program, we provided 30 min more per day during four weeks of either Music-supported Therapy or more time of conventional therapy, where mainly task-specific training was used. Thus, patients in both groups were provided with ten extra hours of training. There are two main differences in training intensity between the previous RCTs and **Study 2**. Firstly, in our study, the standard rehabilitation program was nearly three times more intense than in previous studies. It could be that this standard rehabilitation program is already sufficient and leads to a plateau for improvements. Secondly, in the study of Schneider (2007) and the study of Altenmüller (2009) patients in the control group did not receive extra time of rehabilitation. In contrast, in **Study 2**, we provided an extra time of rehabilitation to the control group so both groups would receive the same amount of training. Thus, it can be concluded that when the number of training hours is equal, there are no differences between Music-supported Therapy and conventional therapy. This can also be interpreted as Music-supported Therapy being able to promote the same amount of motor improvement as traditional approaches.

7.1.2 Effects on motor impairment and activity limitations

As described in the introduction, the ICF framework recognises different levels of functioning, distinguishing the body structure and function to the activities that the individual does (World Health Organization, 2001). In the context of upper extremity hemiparesis after stroke, an alteration in any structure of the motor system and its function is considered an impairment or deficit whereas a problem in performing functional movements when doing tasks is a limitation in activity (Bernhardt, Hayward, et al., 2017). Motor deficits of the upper extremity after stroke manifest as paresis, spasticity and poor spatiotemporal coordination, which in turn affect the performance of functional movements such as reaching, grasping and manipulating objects,

movements that are necessary for daily activities (Jones, 2017; Sharma & Wong, 2016). In this line, the evaluation of the motor deficit and the functional use of the upper extremity in activities should be considered separately as they belong to two different levels of functioning (Bernhardt, Hayward, et al., 2017).

At the body structure and function level, recovery of the motor function means restoring the ability to perform a movement in the same manner as it was performed before the injury whereas compensation is performing old movements in a new way (Levin et al., 2009). The recovery of upper extremity motor deficits in stroke patients is characterised by an increase in the degrees of freedom and velocity, and a reduction of errors (Duff et al., 2013; Van Kordelaar et al., 2014). The evaluation of motor impairment is of paramount importance to know whether true recovery, understood as the restoration of motor deficits, has occurred (Krakauer, 2006). In this thesis, motor deficits were evaluated using (i) the upper extremity subtest of the Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA); (ii) the evaluation of the grip strength; and (iii) 3D movement analysis. Results from **Study 2** and **4** showed that patients treated with Music-supported Therapy increased their score in the FMA, improved their grip strength, enhanced their velocity during a finger and hand tapping tasks and improved their time-to-peak velocity, maximum acceleration and smoothness in a target reaching task (Table 1). In **Study 4**, the patient was in the chronic phase of stroke recovery. While some authors argue that restoration of motor function is unlikely to occur at this stage (Zeiler & Krakauer, 2013), we have observed that even in the chronic phase the patient reduced their motor deficits after Music-supported Therapy. Similar findings in movement kinematics have been found in previous studies validating Music-supported Therapy in subacute (Altenmüller et al., 2009; Schneider et al., 2007; Van Vugt et al., 2014) and chronic stroke patients (Amengual et al., 2013; Rojo et al., 2011). Thus, together with previous results, we found evidence showing that Music-supported Therapy can promote the restoration of motor deficits after stroke.

At the activity level, recovery refers to successful task accomplishment using the end-effectors typically used before the injury. In contrast, compensation refers to performing an activity using alternative strategies such as involving the unaffected hand or using assistive devices (Levin et al., 2009). In this thesis, the patient's ability to perform functional movements was assessed using (i) the Action Research Arm Test (ARAT); (ii) the Arm Paresis Score (APS); (iii) the Box and Blocks Test (BBT); (iv) the Nine Hole Pegboard Test (9HPT); and (v) the Chedoke Arm and Hand Activity Inventory (CAHAI). Patients improved in the performance of these tests after Music-supported Therapy (Table 1). In a similar vein, studies in the subacute and chronic stage have also reported improvements in the functional use of the upper extremity after Music-

supported Therapy (Altenmüller et al., 2009; Ripollés et al., 2016; Schneider et al., 2007; Tong et al., 2015; Van Vugt et al., 2016; Villeneuve et al., 2014).

Table 1. Summary of results regarding the levels of functioning.

ICF Level	Body structure and function (motor function)	Activity (functional use of the upper extremity)
Measures	Fugl-Meyer Assessment of Motor Recovery after Stroke (S2, S4) Grip strength (S2, S4) 3D Movement analysis (S4)	Action Research Arm Test (S1, S2, S4) Arm Paresis Score (S1) Box and Blocks Test (S1, S2, S4) Nine Hole Pegboard Test (S1, S2, S4) Chedoke Arm and Hand Activity Inventory (S2, S4)
Studies	Body structure and function Results (motor function)	Activity Results (functional use of the upper extremity)
Study 1		<ul style="list-style-type: none"> ▪ Patients improved in ARAT, APS and BBT. ▪ No improvement in the 9HPT.
Study 2	<ul style="list-style-type: none"> ▪ Patients in the MST group improved in the FMA after the treatment and in the follow-up, and in grip strength in the follow-up. ▪ Patients in the conventional therapy group improved in the FMA after the treatment and in the follow-up. 	<ul style="list-style-type: none"> ▪ Patients in the MST group improved in ARAT, BBT, 9HPT and CAHAI after the treatment and in the follow-up. ▪ Patients in the conventional therapy group improved in ARAT, BBT, 9HPT and CAHAI after the treatment and in the follow-up.
Study 4	<ul style="list-style-type: none"> ▪ Improvements in grip strength during the second period of MST. ▪ Increased mean velocity in a finger and hand tapping task during the two periods of MST. ▪ Decrease in time-to-peak velocity and increase in acceleration and movement smoothness during the second period of MST in a target reaching task. ▪ No improvement in FMA. 	<ul style="list-style-type: none"> ▪ The patient improved in the BBT and CAHAI at the end of the first MST period and during the second period of MST. Gains were maintained during a withdrawal phase and in the follow-up. ▪ Improvements in ARAT during the second period. ▪ No improvement in the 9HPT in any of the MST periods of training.

The behavioural motor results of the different studies are presented taking into account the different levels of functioning proposed by the ICF. S, study; MST, Music-supported Therapy; FMA, upper extremity subtest from the Fugl-Meyer Assessment of Motor Recovery after Stroke; ARAT, Action Research Arm Test; APS, Arm Paresis Score; BBT, Box and Blocks Test; 9HPT, Nine Hole Pegboard Test; CAHAI, Chedoke Arm and Hand Activity Inventory.

Importantly, since patients also reduced their motor deficits, the gains in the functional use of the upper extremity were not likely due to compensatory mechanisms at the movement level. We could conclude that Music-supported Therapy can reduce motor deficits and improve the functional use of the upper extremity in stroke patients in the same manner as conventional therapy.

7.1.3 Time course of motor gains

One of the aims of **Study 4** was to thoroughly investigate the fine-grained time course of motor improvements during Music-supported Therapy. Since this study was a single-case, its conclusions should be considered as a way to generate new questions in the refinement of the Music-supported Therapy protocol, particularly about its dose-response.

We evaluated the performance of the patient in playing an octave on a keyboard at the end of each training session. We found that improvements in velocity and key pressure were achieved rapidly during the first training sessions, reaching a plateau in performance that lasted for the remaining period of training. Similarly, Villeneuve and colleagues (2013) observed a rapid improvement in note accuracy over the second and third training sessions in chronic stroke patients treated with Music-supported Therapy (Villeneuve & Lamontagne, 2013). Motor skill acquisition is characterised by a fast acquisition stage where rapid improvements in task performance occur during the first training sessions (Karni et al., 1998; Karni et al., 1995; Shadmehr & Brashers-Krug, 1997). The rapid improvement in movement velocity and accuracy accomplished by patients in the musical task performance is reflecting this fast learning stage during the first sessions of Music-supported Therapy.

If gains in instrument playing occurred rapidly, we observed that functional improvements in the standardised clinical motor tests emerged at the end of the Music-supported Therapy program. These functional gains were even more significant after a second training period. When evaluating the motor impairment, we observed a better performance in finger and hand tapping tasks during both periods of Music-supported Therapy. However, in a more difficult task such as approaching the paretic upper extremity to a target, gains were only evidenced during the second period of training.

Overall, these results led us to suggest that (i) rapid improvements occur in the context of musical task performance, (ii) functional gains and recovery of deficits are more evident at the end of the training, and (iii) a second period of Music-supported Therapy promotes major gains at the functional level but also in movements that are more complex. These results may indicate that extending protocols of training in time would allow a more substantial improvement and generalisation to functional and complex movements.

7.1.4 Generalisation of motor gains to daily life activities

The ultimate goal in stroke rehabilitation is to reduce limitations in activities of daily living (Langhorne et al., 2011). The improvement in the performance of daily life activities can be promoted by directly practicing these activities *per se* (i.e. learning how to get dressed again) or by using different activities or tasks (i.e. practising reaching different objects) that allow the training of specific components, such as the motor component, that are needed to perform daily activities (Van Peppen et al., 2004). Most of the rehabilitative techniques to restore upper extremity motor function after stroke fall under the approach of task-specific training (Winstein et al., 2016). However, task-specific improvements are not clinically relevant if they do not

transfer to everyday activities (Kitago & Krakauer, 2013). Thus, in the context of rehabilitation, functional gains in a trained task should generalise to other tasks and contexts to reduce limitations in activities and enhance independence.

Generalisation refers to the process where the effects of the therapy-induced changes spread to a variety of related behaviours (Stokes & Baer, 1977). In other words, generalisation means that training in a specific task can enhance the performance of other tasks unrelated to the training (Reinkensmeyer et al., 2016). In healthy individuals, contradictory evidence exists regarding generalisation of motor learning (Censor et al., 2012; Kitago & Krakauer, 2013); while some studies have shown that procedural learning is task-specific and does not generalise (Berner & Hoffman, 2009; Avi Karni et al., 1995; Rand, Hikosaka, Miyachi, Lu, & Miyashita, 1998) others have demonstrated a transfer effect between arms, visuospatial and motor coordinates (Grafton, Hazeltine, & Ivry, 2002; Kovacs, Mühlbauer, & Shea, 2009; Panzer, Krueger, Muehlbauer, Kovacs, & Shea, 2009; Perez et al., 2007; Perez, Tanaka, Wise, Willingham, & Cohen, 2008; Shea, Kovacs, & Panzer, 2011). The conditions under which generalisation of motor learning occurs are not fully understood. Transfer effects between tasks may depend on how many elements these tasks share and practice variability during the training (Censor et al., 2012).

For the first time in the literature validating Music-supported Therapy, the patient's ability in performing activities of daily living has been measured in **Study 2** and **4**. The idea behind Music-supported Therapy is to use a paradigm of motor skill learning to recover from motor deficits of the upper extremity but with the ultimate goal that gains in mobility allow the patient to perform better in their daily lives (Schneider et al., 2007). Other therapeutic interventions to improve the motor function after stroke have shown little generalisation of treatment effects (Kwakkel et al., 2004) and still of much debate is that if stroke patients show impaired motor learning (Kitago & Krakauer, 2013).

We used the CAHAI to evaluate the patient's performance in activities of daily living. In this test, patients are asked to open a jar of coffee, make a phone call, pour a glass of water, do up five buttons, dry back with a towel or clean a pair of eyeglasses among other tasks that involve manipulating daily objects. Compared to the ARAT, BBT and 9HPT, which evaluate functional movements, the CAHAI allows studying how these functional movements are integrated into an activity that has real-world meaning.

Study 2 and **4** showed that patients treated with Music-supported Therapy improved in their performance of activities of daily living. However, as mentioned before, in **Study 2**, patients treated with conventional therapy also showed an improvement in the performance of these activities. It could be argued that conventional rehabilitation is responsible for the transfer effect

to activities of daily living. In that case, it would be expected that patients in the control group would show a more significant improvement in activities of daily living since they were receiving more time of conventional rehabilitation but as mentioned, no differences were found between groups. Moreover, in **Study 4**, the patient was only treated with Music-supported Therapy and showed an enhancement in daily tasks. In a previous study, subacute stroke patients treated with Music-supported Therapy reported generalisation of the training effect on every-day functions (Schneider et al., 2007). Therefore, the improvement in musical task performance and motor gains after Music-supported Therapy seems to generalise to functional tasks and activities of daily living.

7.1.5 Retention of motor gains

Rehabilitation not only aims at reaching an optimal functional level but also at maintaining it. This means that motor training in stroke should promote the acquisition and consolidation of movement patterns, and importantly, their long-term retention. The presence of reward and variety in practise structure and context during training are crucial aspects that influence successful consolidation and contribute to the retention of well-learned movement sequences in the absence of training (Abe et al., 2011; Caroni, Donato, & Muller, 2012; Dobkin, 2004; Magill & Hall, 1990; Savion-Lemieux & Penhune, 2005; Shea & Morgan, 1979).

The striatum, the ventral tegmental area and the hippocampus are involved in reward-dependent motor memory stabilisation through dopaminergic modulations and long-term potentiation (Dayan & Cohen, 2011). Music-supported Therapy can be viewed as a rewarding activity on different levels. On the one hand, the auditory feedback serves as a reinforcer in successful trials that along with the feedback of the therapist can contribute to the consolidation of motor patterns (Sugawara, Tanaka, Okazaki, Watanabe, & Sadato, 2012; Wilkinson et al., 2015). On the other hand, musical activities are experienced as joyful and rewarding for most individuals, capable of inducing strong emotional responses and activate the rewarding dopaminergic system (Salimpoor et al., 2013). Moreover, the use of musical instruments during training facilitates variety in practice and context. Stroke patients can play a wide variety of musical sequences and melodies, which require the combination of different finger and hand movements. Using more than one instrument also allows introducing the element of contextual variety in Music-supported Therapy.

Two studies in this thesis examined the retention of motor gains (**Study 2** and **4**) after Music-supported Therapy and found that improvements were maintained three months after finishing the training. Thus, gains in the functionality of the upper extremity and the reduction of motor

impairment were maintained over time. In **Study 2**, this result was also found in the control group, who showed retention of motor improvements. Considering the non-superiority effect of Music-supported Therapy over conventional approaches, we can conclude that adding Music-supported Therapy to the standard rehabilitation program promotes the same retention of gains as conventional therapy at three months. In the design of new therapies for stroke rehabilitation, it is especially important to consider if the effects of these therapies are maintained over time. Future studies investigating Music-supported Therapy should explore if motor improvements are maintained beyond months poststroke.

7.2 Effects on cognition, mood and quality of life

In **Study 2**, we found that patients treated with Music-supported Therapy reported having better language abilities than those patients who were treated only with conventional therapy. A within-group analysis revealed that patients in the Music-supported Therapy group increased their rate of verbal learning after the therapy. The study of Ripollés and colleagues (2016) also observed a similar effect on the rate of verbal learning in chronic stroke patients after Music-supported Therapy (Ripollés et al., 2016). Music follows a hierarchical structure and requires the perception and integration of acoustic features such as pitch and rhythm, aspects that share similarities with language. Our result fits with the OPERA hypothesis, which proposes that musical training can enhance speech (Patel, 2011). Patel (2011) suggests that there are five conditions of musical training that induce plasticity in language networks: (i) music and language share many functional neural networks, (ii) the processing of music is more demanding; (iii) music induces positive emotions; (iv) musical activities are frequently repeated, activating these networks; and (v) require focused attention. These elements may explain why Music-supported Therapy can have a transfer effect on language. The results of **Study 2** led us to conclude that Music-supported Therapy indirectly boosts language abilities in stroke patients. Given the positive effect of Music-supported Therapy on language, it would be interesting to investigate if this therapy is effective in improving language abilities in those patients with aphasia or dysarthria.

Although playing a musical instrument places high demands on cognitive functions, such as attention, executive functions or working memory, we did not find any other enhancement of cognitive functions aside for the improvement in the rate of verbal learning. It could be that since the target of the therapy is not the cognitive function, the effect that Music-supported Therapy can have on this domain is so small that is hard to find between-group differences. However, other lines of research with music-based interventions in stroke have found positive effects on this domain. Specifically, daily music listening leads to an enhancement of verbal

learning and focused attention in acute stroke patients (Särkämö et al., 2008). Another possible explanation for this lack of results at the cognitive level in our studies is that it could be that the neuropsychological tests used were not sensitive enough. Future studies should include a more comprehensive neuropsychological evaluation to investigate the effects of Music-supported Therapy on cognition.

Regarding the mood and quality of life outcomes, in **Study 1** and **2**, we found that patients treated with Music-supported Therapy improved their quality of life and health-related quality of life. However, in **Study 2**, these improvements were not found as an interaction effect between groups. A within-group analysis revealed that patients were less fatigued and had less negative emotions after Music-supported Therapy. Our results are in line with those from Van Vugt and colleagues (2014) who observed a reduction of fatigue and depressive symptoms in subacute stroke patients treated with Music-supported Therapy (Van Vugt et al., 2014). In chronic stroke patients, an increase in arousal, valence, positive affect and quality of life as well as a decrease in depression have been reported after Music-supported Therapy (Ripollés et al., 2016).

It could be argued that improvements in mood and quality of life are related to gains in functionality. If Music-supported Therapy is able to improve the functionality of the upper extremity and the autonomy of patients in activities of daily living, we could expect that these improvements will positively affect the patient's quality of life. An improvement in the performance of activities of daily living could lead to a reduction in the disability experienced. However, in **Study 2**, motor gains were also present in the control group but only patients treated with Music-supported Therapy reported better mood and quality of life. This reinforces the idea that an enhancement in mood and quality of life is due to music. Music is a powerful, pleasurable stimulus that can induce positive feelings and can be used for emotional self-regulation (Laukka, 2007). Moreover, in Music-supported Therapy, patients are learning a new skill that has real-world relevance, which could increase feelings of self-efficacy and agency, having an impact on their mood and quality of life. Specifically, health-related quality of life is the perception of one's position in life, influenced by impairments and functional status (Patrick & Erickson, 1993). Providing a therapeutic activity where patients can experience they are learning something new regardless their motor impairment may change this perception of disease and disability.

The results on mood and quality of life are of great significance because one of the aims of stroke rehabilitation is to improve the patient's quality of life (Albert & Kesselring, 2012). If Music-supported Therapy can promote similar motor improvements as conventional therapy but

patients are in a better mood and increase their quality of life, this argues in favour of Music-supported Therapy over conventional approaches.

7.3 The role of musical reward in Music-supported Therapy

In **Study 2**, we observed that the capacity of patients to experience pleasure with musical activities was related to motor gains in those patients treated with Music-supported Therapy. This association was not found in the control group that underwent conventional rehabilitation. The reward that patients experience in musical activities was evaluated using the Barcelona Music Reward Questionnaire (Mas-Herrero et al., 2013). Specifically, the factor that was related to motor gains in the Music-supported Therapy was the sensory-motor one. This means that those patients who often dance when they listen to music, cannot help to tap or move when listening to melodies and hum or sing along to music were the ones that improved more in the Music-supported Therapy group.

No previous study has addressed the role of musical reward in the training success of Music-supported Therapy. The fact that patients who are more sensitive to experience reward in musical activities improved more during Music-supported Therapy agrees with recent proposals in the field of motor learning (Wulf & Lewthwaite, 2016). Intrinsic motivation towards the task is a crucial component for reward-based learning and successful motor performance (Censor et al., 2012). In this line, it is not surprising to find that when testing the most sophisticated and modern methods of motor rehabilitation such as virtual reality, simple recreational activities have shown to be more effective (Saposnik et al., 2016).

In the literature of stroke motor rehabilitation, it is always pointed out that rehabilitation should motivate and engage the patient (Langhorne et al., 2011). However, evaluating whether patients are enjoying the task they are doing in rehabilitation centres is difficult since motivation is a complex behavioural factor (Maclean, Pound, Wolfe, & Rudd, 2000). A systematic review of qualitative studies found that stroke patients usually experience rehabilitation as boring (Luker et al., 2015). Rehabilitation is a patient-centred process, and therapeutic activities should be chosen in collaboration with the patient, recognising their autonomy and motivation (Wressle et al., 2002). Our findings point out the need for individualisation when selecting the rehabilitative interventions regarding the patient's preferences and their enjoyment towards the task in order to boost motor learning and performance.

7.4 Mechanisms of brain plasticity associated with Music-supported Therapy

Understanding the mechanisms that underpin rehabilitative interventions and allow functional recovery is one of the biggest challenges in stroke rehabilitation. Frequently, stroke rehabilitation is regarded as a 'black box' (DeJong, Horn, Conroy, Nichols, & Heaton, 2005). We are able to clinically characterise patients, their anatomical damage and their deficits. Moreover, we are able to observe their improvements and measure them quantitatively. However, little is known as to what are the active ingredients in the rehabilitation process that allow behavioural improvements and which are the plastic mechanisms responsible for them. From a computational point of view, recovery after stroke can be seen as a constrained optimisation problem, where the constraint for recovery is the amount and type of anatomical damage (Reinkensmeyer et al., 2016). Neural plasticity acts to amend these constraints by involving intact brain regions to support functioning. Motor learning and rehabilitation would be the optimisation in this computational problem since it aims to modulate neural plasticity (Reinkensmeyer et al., 2016).

During the initial weeks post-stroke, there is a period of increased plasticity where internally generated stimuli induce changes at the molecular, cellular and synaptic level that lead to an excessive production of new synapses and increased excitability (Buma et al., 2013; Carmichael et al., 2005; Krakauer et al., 2012). These processes create a favourable environment for experience-dependent plasticity, where reorganisation of cortical motor maps are the neural substrate of recovery (Buma et al., 2013). Rehabilitation after stroke aims to boost the endogenous plastic mechanisms and induce experience-dependent plasticity through two main approaches: training and enriched environment.

Music-based interventions can incorporate these two approaches since musical activities can be used as a form of training to promote motor skill learning in stroke patients and because these activities are varied and rich in stimuli (Zimmerman & Lahav, 2012). Enriched environment is a concept that emerged from research in animal models, and it has been shown to promote neurogenesis, dendrite spine growth and synaptogenesis (Biernaskie, 2004; Biernaskie & Corbett, 2001; Hicks et al., 2007; Livingston-Thomas et al., 2016). Its equivalent in stroke rehabilitation would be multimodal stimulation (Pekna et al., 2012). Musical activities have a multisensory nature, where auditory, visual and somatosensory stimuli need to be processed. Moreover, they involve motivation and emotional aspects that may boost the patient's engagement in training, having a positive impact on learning (Herholz & Zatorre, 2012; Särkämö et al., 2013).

Two studies in this thesis, **Study 1** and **3**, examined the plastic changes induced by Music-supported Therapy using Transcranial Magnetic Stimulation and functional Magnetic Resonance Imaging, respectively. In **Study 1**, we found that the excitability of the affected sensorimotor cortex increased its activity and cortical motor map reorganisation occurred in subacute stroke patients after Music-supported Therapy. Our results are in agreement with the study of Amengual and colleagues (2013) where similar findings in the excitability of the sensorimotor cortex and reorganisation of motor maps were reported after Music-supported Therapy in chronic stroke patients (Amengual et al., 2013). Changes in excitability are common after stroke. Neurons that surround the lesion become hypoexcitable, increasing their thresholds for excitation and affecting the interhemispheric balance (Groppa et al., 2012; Traversa et al., 1998). A return to a more normal pattern of threshold excitability might indicate functional restitution in the affected hemisphere (Kobayashi & Pascual-Leone, 2003). Regarding cortical motor map reorganisation, we observed a posterior displacement of the map after the training with Music-supported Therapy. It has been well documented that training after stroke can induce cortical motor map expansions to adjacent areas that are associated with recovery (Jaillard et al., 2005; Nudo & Milliken, 1996). Music-supported Therapy was designed with a strong ground in basic research. The musician's brain has been an excellent model to study neural plasticity, and Music-supported Therapy aims to induce similar plastic changes than those taking place when healthy individuals learn to play an instrument (Rodriguez-Fornells et al., 2012). When learning to play an instrument, cortical motor maps are expanded in response to the demands of complex fine movements (Pascual-Leone et al., 1995; Schlaug, 2015). With time, the refinement of connections occurs, and only the most efficient ones are left after activity-based pruning of new synapses (Dayan & Cohen, 2011). The main limitation derived from **Study 1** is the lack of a control group of patients receiving a different treatment. This aspect limits the scope of our conclusions since we could not demonstrate that these changes were specific to Music-supported Therapy. In this line, other rehabilitation techniques can promote similar changes in the reorganisation of the sensorimotor cortex (Liepert, 2010; Liepert et al., 1998).

In **Study 3**, apart from studying the plastic changes induced by Music-supported therapy compared to conventional treatment, we also aimed to characterise the sample and study the relationship between corticospinal tract integrity and motor recovery. Considering the previous analogy of rehabilitation as a constraint optimisation problem, the lesions and white matter damage of patients are related to the anatomical constraint of recovery (Reinkensmeyer et al., 2016). We evaluated a subsample from **Study 2**, which was an RCT that tested the effectiveness of adding Music-supported Therapy to the standard rehabilitation program. The design used in **Study 2** is regarded as the gold standard in clinical research since randomisation, and the presence of a control group allow to rule out potential confounding variables. However, the

lesion location and the extent of white matter damage, especially in the corticospinal tract, are important aspects that influence recovery (Winters, Van Wegen, Daffertshofer, & Kwakkel, 2015). Having this in mind, we explored if the samples recruited in **Study 2** were comparable at the neural level. We found that both groups mainly had subcortical lesions and no differences were found in the distribution and amount of white matter damage between patients. This is of particular clinical relevance because it suggests that the behavioural results obtained in **Study 2** were not modulated by differences in the patients' lesions. However, contrary to what we expected, the integrity of the corticospinal tract, measured with the Tractotron software, did not correlate with motor recovery. We interpreted this lack of finding as a limitation in the method used. Other neuroimaging approaches such as tractography using diffusion tensor imaging would be more appropriate to study white matter integrity at the individual level (Rosenzweig & Carmichael, 2015; Sozmen, Hinman, & Carmichael, 2012).

In **Study 3**, plastic changes were assessed using a motor task in a functional Magnetic Resonance Imaging evaluation before and after the intervention. In this task, patients had to perform sequential tapping movements with either the affected or unaffected hand. The only difference we found between groups was that patients treated with Music-supported Therapy showed more activation in the middle and superior temporal gyri and insula of the affected hemisphere after the training. Although some of these regions correspond to associative auditory cortices, we cautiously could not consider that this indicated a reestablishment of audio-motor coupling because of the high threshold used in the analysis (uncorrected $p < 0.005$) (Ripollés et al., 2016). We had hypothesised that bilateral activations would be reduced in the Music-supported Therapy group since the therapy aims to promote reorganisation within the affected hemisphere (Ripollés et al., 2016). However, no differences were found between groups in the reorganisation of motor areas. This lack of finding can be interpreted as Music-supported Therapy promoting similar plastic changes as conventional therapy, which is in agreement with what we found at the motor level. As discussed before, there are no differences between Music-supported Therapy and conventional therapy in improving the motor ability and reducing the motor deficits of the upper extremity after stroke. Future studies should evaluate other aspects that might be specific to Music-supported Therapy such as its ability to re-establish the audio-motor coupling in stroke patients. Connectivity analysis can provide a valuable insight about the changes at a network level that might offer a more comprehensive perspective of plastic changes promoted by Music-supported Therapy.

7.5 Clinical considerations for implementation

Music-supported Therapy, like other motor rehabilitation techniques, can be regarded as a complex intervention. The therapy comprises numerous elements, all of them contributing to treatment success, which are difficult to study separately. Some of these elements of complexity rely on the multimodal nature of the training or the fact that the therapist and patient's behaviour may influence the treatment effect. As we have observed, those patients who like music more, are the ones who had major motor improvements after Music-supported Therapy. Moreover, the training program is tailored to the needs of the patient, and although the main target of the therapy is the recovery of the motor function, it can affect other areas of functioning. Taking into account the Medical Research Council framework for developing, evaluating and implementing complex interventions, here I discuss clinical aspects of Music-supported Therapy for its implementation into clinical practice.

7.5.1 Developing and redefining Music-supported Therapy

Stages in the process of developing, evaluating and implementing complex interventions are not linear, and redefinition of treatment and how it can affect the outcome can be done at any time to include the latest evidence.

Music-supported Therapy was first designed by Schneider and colleagues (2007), but Rodríguez-Fornells and collaborators (2012) later delineated its principles as (i) mass repetition of finger and arm movements; (ii) audio-motor coupling and integration; (iii) shaping; and (iv) emotion-motivation effects (Rodríguez-Fornells et al., 2012). Considering the latest literature on motor learning, other aspects are highlighted in an effort of complementing the definition and the relevant elements of Music-supported Therapy (Figure 1).

Task-specific: Music-supported Therapy is explicit and goal-directed training. It aims at learning a specific skill, playing musical instruments, through practice and training to promote the acquisition, consolidation and long-term retention of motor patterns of the upper extremity in stroke patients.

Task relevance: learning to play an instrument is an activity that has real-world relevance. There are individual differences in musical reward that influence the treatment success. Music-supported Therapy is more effective in those patients who like music more. The recognition of patient's motivation and their enjoyment towards the therapeutic activity is a critical element in the patient-centred process of rehabilitation that contributes to successful motor learning.

Instructional language and guidance: in Music-supported Therapy, the therapist provides instructions and guidance that should be autonomy-supportive. Instructions can be easily directed to the outcome of the performance, which is the sound of the musical instrument, focusing the attention on the goal of the movement.

Prompting: the therapist can use verbal and visual cues to prompt the patient's movements and play notes to guide the patient to initiate the performance. Similarly, electronic instruments can also be programmed to provide cues for patients (i.e. metronome).

Modelling: sequences or melodies can be demonstrated to the patients by the therapist or making use of audio recordings. Most electronic instruments allow recording sequences that can be used during the training. Modelling can also be graded in difficulty. The therapist might show how to play, providing visual and auditory information that facilitates imitation. However, only listening to sequences to reproduce them might be more challenging for the patient.

Reinforcement: there are extrinsic and intrinsic reinforcers in Music-supported therapy that contribute to reward-based learning. The feedback of the therapist and the auditory stimulus are sources of information about performance that are extrinsic reinforcers. The therapist can provide information after good trials to stress successful performance. The auditory stimulus is a crucial component of the training since it can be used to adjust future performance and to compare the actual performance with movement and outcome predictions in a feedforward and feedback loop. Both the therapist and also the auditory stimuli can increase errors awareness to promote online motor adjustments. As the patient progresses, the feeling of success can act as an intrinsic reinforcer, inducing feelings of self-efficacy, satisfaction, and positive affect, and increasing motivation.

Shaping and chaining: musical instruments offer a wide range of possibilities to adapt exercises to the degree of patient's motor impairment. In Music-supported Therapy, the training program is a stepwise regime with exercises that increase in complexity. Patients may start playing simple sequences until they learn to play melodies. This aspect allows tailoring the treatment to the individual needs of each patient and also reduce the perceived task-difficulty.

Fading: the therapist can progressively remove cues as the patient progresses to support their autonomy.

Autonomy: Music-supported Therapy offers a setting where the patient can decide several aspects. For instance, these opportunities for choice can be which sequences and melodies to play or when to make a short break. The training provides a context where the patient is an

active agent in control of the musical instrument, promoting active learning, which can increase self-efficacy beliefs and perceptions of competence.

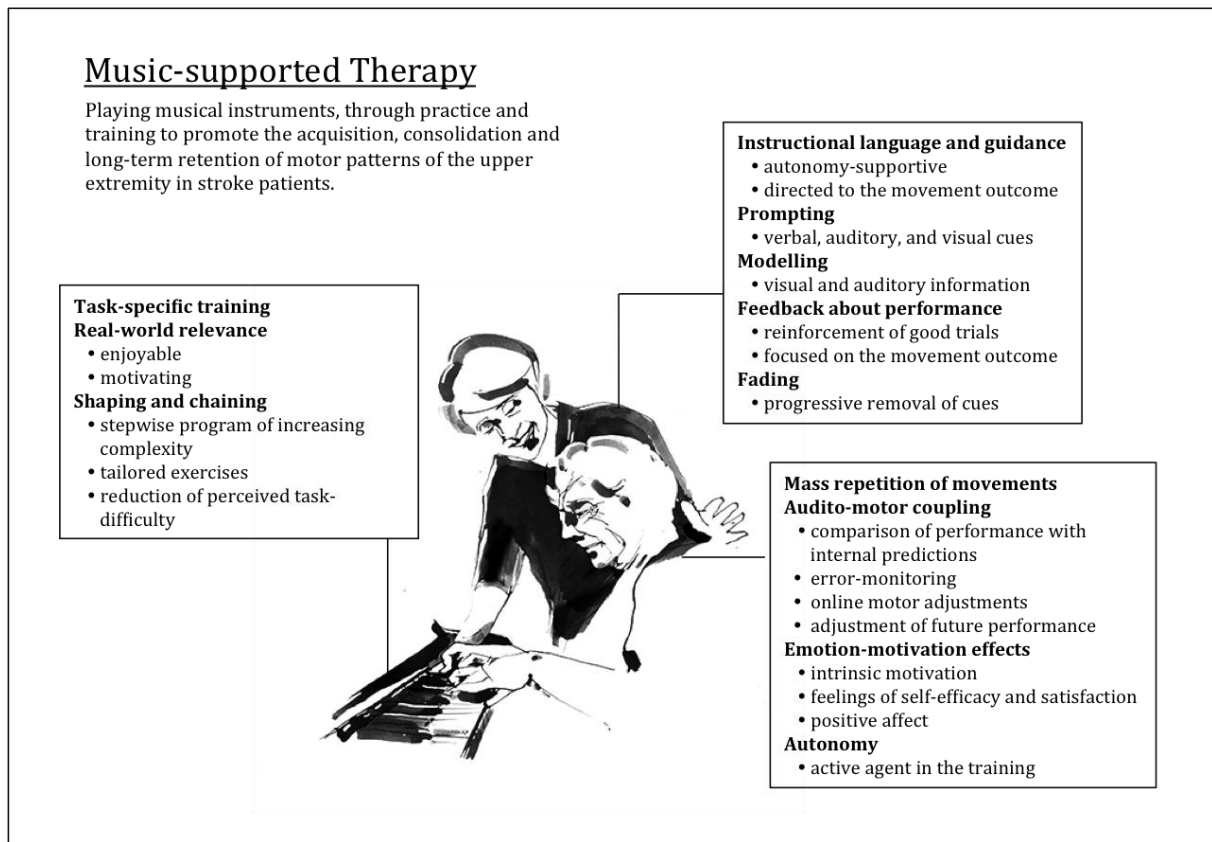


Figure 1. Elements of Music-supported Therapy.

All these aspects may contribute to creating the optimal conditions that facilitate effective learning and motor performance. Music-supported Therapy integrates many principles of stroke motor rehabilitation and motor skill learning. It is an activity that has real-world relevance and entails mass repetition of movements, a set of varied exercises with graded difficulty and close interaction with the therapist who models movements and provides instructions, guidance and feedback (Schneider et al., 2007). Importantly, the sound produced by the musical instrument serves as valuable information for the motor system since it provides feedback about the performance and allows the comparison of the movement result with internal predictions (Rodriguez-Fornells et al., 2012). Music-supported Therapy can impact motivation by providing autonomy to the patient and increasing expectancies for successful motor performance. Moreover, it is relatively likely that the patient adopts an external focus of attention, paying attention to the sound of the instrument and thus, inducing automaticity in movements and implicit learning. All these motivational and attention aspects enhance goal-action coupling, positively impacting motor learning and performance (Wulf & Lewthwaite, 2016).

Regarding the redefinition of outcomes affected by Music-supported Therapy, the training has already proven to enhance the motor function and reduce motor impairment in stroke patients. Moreover, it can indirectly boost language abilities and impact mood and quality of life. The underlying plastic mechanisms that support the change in motor function are reorganisation within the lesioned hemisphere, with changes in cortical motor map and excitability. Future studies should explore the effect of Music-supported Therapy on improving participation, changing the patient's experiences of disability and reducing the caregivers' burden, aspects that have not yet been investigated. Moreover, a thorough study of the neuroplasticity promoted by the therapy is needed to understand the mechanisms that subserve behavioural improvements.

7.5.2 Piloting, feasibility and evaluating Music-supported Therapy

Music-supported Therapy seems feasible to apply, since it has already been tested at a group level in different studies in the subacute and chronic phase of stroke recovery (Altenmüller et al., 2009; Ripollés et al., 2016; Schneider et al., 2007; Tong et al., 2015; Van Vugt et al., 2016). Voluntary withdrawal of patients undergoing Music-supported Therapy has rarely been reported although further research is needed to investigate patients' satisfaction or intention to continue. Moreover, the acceptability of the therapy by therapists and stakeholders is still unknown. Aspects such as the perceived appropriateness and suitability within organised stroke rehabilitation influence the extent to which a treatment is likely to be used. Focused groups, measures of satisfaction in RCT designs or surveys before and during the intervention can provide insight into all these aspects that influence acceptability (Bowen et al., 2009).

7.5.3 Reporting the results and implementing Music-supported Therapy

For Music-supported Therapy to be included in clinical practice guidelines, two aspects need to be considered. The first aspect is the number of published studies and their level of evidence. Currently, only five RCTs have validated Music-supported Therapy, including **Study 2** of this thesis, four experimental non-randomised studies, one case series and two case-studies (Table 2). Future efforts should be directed to conduct multiple RCTs and meta-analyses. The quality of these studies will contribute to gain certainty of the treatment effect and have Level A evidence. The second aspect when evaluating Music-supported Therapy is the size of the treatment effect. Music-supported Therapy seems useful and effective in treating hemiparesis of the upper extremity after stroke. However, conflicting evidence exists regarding its superiority over conventional therapy. In **Study 2**, when controlling for the number of hours, Music-supported Therapy promoted the same motor improvement as conventional therapy whereas other studies have shown a superiority effect. The balance between the benefit and risk and which is the size

of the treatment effect is a critical aspect to be further investigated. This aspect will influence the strength of the clinical recommendations to apply Music-supported Therapy. Moreover, studies evaluating the cost-effectiveness of the therapy are necessary to allow the transition of Music-supported Therapy from research to clinical practice.

Table 2. Available studies validating Music-supported Therapy.

RCTs	Experimental studies	Case series Case-study
Study 2 – Grau-Sánchez et al., 2018 Tong et al., 2015 VanVugt et al., 2016 Altenmüller et al., 2009 Schneider et al., 2007	VanVugt et al., 2014 Ripollés et al., 2016/Amengual et al., 2013 Study 1 – Grau-Sánchez et al., 2013 Villeneuve et al., 2014	Study 4 – Grau-Sánchez et al., 2017 Villeneuve et al., 2013 Rojo et al., 2011

Implementation is challenging because aspects such as practicality, adaptation, and integration of the therapy in rehabilitation program and centres have to be addressed. To implement Music-supported Therapy, an analysis of the resources regarding space, materials and therapist needed should be done. Even in some cases, unexpected factors can affect implementation in real practice. Moreover, monitoring of implementation to ensure the quality of administration or how the therapy is adapted to clinical practice will be necessary during the first years after introducing Music-supported Therapy in clinical settings.

7.6 Strengths and limitations of the present work

This work contributes to the existing evidence in the field of music-based interventions in stroke rehabilitation. We have addressed aspects regarding the effectiveness of Music-supported Therapy that were unexplored until now such as the retention of motor gains, generalisation of motor gains to activities of daily living and the role of musical reward in the treatment. One of the main strengths of this thesis is the use of different research designs, suited to test different research questions. Using an interventional experimental design, an RCT and a single-case methodology, we have explored different relevant clinical aspects at a group and individual level.

Each of these methodologies has its own advantages and disadvantages and we could complement the results obtained in the different studies. For instance, in **Study 1**, the size of the sample and the lack of a control group of patients undergoing a different intervention were aspects that limited the scope of our conclusions. By contrast, in the RCT (**Study 2**), the sample was bigger, which contributes to a better generalisation of results to the stroke population, and Music-supported Therapy was compared to conventional treatment. This example illustrates

how aspects that we could not consider or control in **Study 1** were solved in **Study 2**. RCTs are regarded as the gold standard design in clinical research, and their results are considered at a group level and come from a highly-controlled setting (Friedman et al., 2015). However, this type of design is not suited to answer which patients are going to benefit more from the treatment. Moreover, the controlled setting may not mimic real-life conditions (Iwakabe & Gazzola, 2009; Sanson-Fisher, Bonevski, Green, & D'Este, 2007). The use of a single-case design in **Study 4** allowed us to address these aspects and explore the effects of Music-supported Therapy at an individual level and consider personal factors of the patient that may have an influence on the treatment effect (i.e. past profession or how much the patient enjoys musical activities) (Sarre et al., 2014). Thus, we complemented the results from the RCT with a single-case study.

Apart from overcoming the limitations of designs by using different ones that are complementary, there were new scientific questions that emerged from studies and were included as the thesis progressed. For example, in **Study 1**, there were aspects that we could not include in the design and thought that we important to address in the following studies. For instance, we found an improvement in the motor function but we did not measure the ability of patients to perform activities of daily living with the affected extremity after the treatment. Moreover, we only evaluated patients right after the intervention and could not investigate the retention of motor gains. With the practical experience we gained conducting **Study 1**, we thought that motivation may play an important role in the treatment effect. All these aspects were considered in the subsequent studies and we included an evaluation of activities of daily living (CAHAI), a follow-up evaluation at 3 months and a questionnaire that measured musical reward in both **Study 2** and **4**.

A major limitation of the present thesis is that samples were recruited at the same rehabilitation centre within each study. Rehabilitation services and programs for subacute stroke patients can vary across centres even in the same region or country (Winstein et al., 2016). The type of setting, rehabilitation duration and intensity, or therapists involved are contextual factors that influence the recovery process in stroke patients (Alford et al., 2015; Vargus-Adams & Majnemer, 2014). Rehabilitation is a complex process and most of the mentioned contextual factors cannot be controlled. A solution to this problem is to conduct multicentre studies. Future studies should recruit patients at different centres to allow generalisation of results regardless of the contextual factors that affect the patient with the aim of improving the external validity of results.

An intrinsic limitation in the recruitment is linked to the fact that participation in studies is voluntary. Stroke patients that are more active, open to new experiences or motivated with the

rehabilitation process are more likely to accept to participate. Although participants can withdraw from studies at any point, participating means completing a month of an extra therapy and an extensive evaluation before and after the treatment. All these procedures may seem daunting for stroke patients and it could be that patients with apathy or those that are more depressed or fatigued refuse to take part in the studies. This entails a bias in the sense that results are influenced by the emotional state and motivation of the patient. A possible way to overcome this issue in the future is to conduct studies with bigger samples that allow investigating what is the treatment response of patients enrolled in the studies that have lowered mood. Moreover, evidence and experience gathered from studies in mental illness may provide insights about the most optimal strategies to encourage patients with lowered mood to participate in studies.

The samples of the studies were heterogeneous, which can be seen as a strength and limitation at the same time. On the one hand, having a heterogeneous sample is more representative of the stroke population, contributing to the external validity of studies and generalisation of results. On the other hand, several clinical aspects within the stroke sample may act as confounding variables. For instance, the type of stroke, the degree of motor impairment, the lesion location or the amount of white matter damage are important predictors for recovery since they influence the extent of recovery a patient can achieve (Bernhardt, Borschmann, et al., 2017). Although we could collect most of this information from medical records and through the studies' evaluations, we could not run analyses to test the effectiveness of Music-supported Therapy in different subsamples (i.e. patients with cortical lesions vs. patients with subcortical lesions, patients severely affected vs. patients with slight hemiparesis). Samples were not that big to have comparable subgroups that allowed us to explore the influence of the mentioned clinical variables. In the future, studies should stratify patients considering these biomarkers to underpin which target within the stroke population responds better to Music-supported Therapy.

Regarding the evaluation of participants, we selected the most widely used clinical and behavioural tests in stroke motor rehabilitation, which allows the comparison and integration of our results into the existing literature. Moreover, the participants' evaluation remained similar across studies, giving us the opportunity to integrate the results we have obtained. At the same time, we used several techniques, such as three-dimensional movement analysis, transcranial magnetic stimulation or functional magnetic resonance imaging, studying different levels of functioning, from behaviour through brain structure and function.

We did not measure the amount of physical activity or participation in other activities outside the context of rehabilitation, which has a direct influence on the patient's recovery. A possible way to control this factor is to include questionnaires or semi-structured interviews and quantitatively measure the amount of activity the patient does. Thus, in future studies, this variable could be included in the analyses as a covariate to weight its effect on the outcome.

7.7 Future directions in Music-supported Therapy research

There are still several questions regarding Music-supported Therapy that need to be addressed before implementing this treatment into clinical practice. Aspects related to the training protocol, the evaluation of patients, the research methodology and the process of implementation are mentioned in this section in order to move Music-supported Therapy forward.

7.7.1 Modifications to the protocol

The results of this thesis suggest that extending the Music-supported Therapy protocol can lead to more substantial motor improvements. However, this conclusion needs to be sustained and tested at a group level. The number of sessions in previous studies ranged from nine to twelve with protocols proving a total of 5, 7.5, 9 and 10 hours across three or four weeks (Altenmüller et al., 2009; Ripollés et al., 2016; Schneider et al., 2007). The selection of the number of sessions, the number of training hours and their distribution seems arbitrary in previous studies. Evidence from basic research on motor learning can help in the design of the most optimal protocol regarding dosage for future studies.

We have used a protocol that consisted of daily short sessions, but it could be that distributing practice, leaving space to bigger rest periods, and providing longer and more intense sessions lead to a better motor performance in stroke patients (Krakauer, 2006; Shadmehr & Brashers-Krug, 1997). Future studies, especially in the form of single-case designs, should explore the benefits of resting between sessions and the role of offline periods to boost motor memory consolidation (Doyon & Benali, 2005).

The implementation of Music-supported Therapy can be improved by providing therapists with a standardised manual for instructional language that is autonomy-supportive, and information about the type and appropriateness of feedback during the training (Wulf & Lewthwaite, 2016). Moreover, modifications to the protocol that allow the patient to select the type of instrument, or their most preferred songs or musical style could increase the patients' motivation and feeling of

autonomy. Since motor improvements are related to the individual's capacity to experience reward from musical activities, future studies should consider stratifying patients with regard to this aspect.

Individual sessions in inpatient rehabilitation centres or day hospital services are sometimes difficult to adopt and are constrained by the resources of health systems or insurance conditions. Music-supported Therapy can also be adapted to apply it at the patient's home, as a part of a community reintegration model (Villeneuve et al., 2014). The use of technology may also allow introducing new elements in training such as modelling with videos or self-modelling by hearing the best trials played by the patient. The development of new technologies that allow tailoring exercises and monitoring patients' progress virtually could be of great significance for using Music-supported Therapy as a form of telerehabilitation. However, one difficulty when applying Music-supported Therapy at home could be that it may only work for already motivated patients.

7.7.2 Evaluation of patients

Regarding the evaluation of patients, future studies should use other neuroimaging techniques to investigate thoroughly the plastic mechanisms that underpin the improvements in Music-supported Therapy. A critical question about Music-supported Therapy is in which stage of motor recovery is more appropriate to apply it. Most studies have been performed in the early subacute phase when the potential for recovery and endogenous mechanisms are at their maximum expression (Dancause & Nudo, 2011). However, the recreational nature of Music-supported Therapy makes it feasible to apply it in the chronic stage as a therapy aimed at maintaining the motor function, but more studies are needed to sustain this conclusion.

We have only investigated the retention of motor gains three months after finishing the training but longer follow-ups should be performed. Evaluation in the long-term can also explore the negative side-effects of Music-supported Therapy (Craig et al., 2008). Since Music-supported Therapy uses a paradigm of motor learning, trying to avoid compensatory movements and promote recovery of the motor function, it could be that patients experience problems such as pain or muscle contractions, due to the forced used of effectors (Carmichael & Krakauer, 2013; Jones, 2017). We have seen a transfer effect to language abilities, but it could be that musical training also promotes the enhancement of other cognitive functions other than language (Särkämö, 2016). Future studies may explore the effects on other cognitive functions using more sensitive neuropsychological tests.

7.7.3 From the laboratory to the clinic

Music-supported Therapy was designed in 2007 with a strong ground on basic research. By using the musician's brain as a model for neuroplasticity, the rationale behind Music-supported Therapy was to use elements of musical training to promote brain reorganisation and functional recovery in stroke patients. However, there is a long process between the design of a treatment and its implementation into clinical practice routinely.

From the first study of Music-supported Therapy by Schneider and colleagues (2007) to the present day, other studies have evaluated several aspects related to the effectiveness of this therapy. A common thought adopted by most basic researchers and enthusiasts of music therapy may be that a decade of research is enough for administering a rehabilitative treatment. However, introducing Music-supported Therapy into clinical guidelines will require more high-quality RCTs, with larger samples, stratification of patients and recruitment at multiple rehabilitation centres. Only this will allow conducting meta-analyses and systematic reviews to finally reach a conclusion about its effectiveness.

The cost of Music-supported Therapy has never been evaluated, but it is a crucial aspect when implementing therapies that have been designed in the laboratory and need to be adopted in centres that belong to the public health system or involve health insurance companies. Once the therapy is included in clinical practice guidelines and implemented into clinical practice, further studies will be needed to monitor the administration of Music-supported Therapy, its adaptation and integration into real practice and its long-term effects, aspects that are difficult to explore using research designs.

Although it may seem a daunting process, it is our obligation as clinical scientists to systematically follow the arduous process of designing and implementing complex interventions to provide the best evidence for clinicians, which ultimately will impact the treatment quality that individuals with stroke receive in one of the most challenging moments of their lives.

Conclusions

Chapter 8. Conclusions

The present doctoral thesis has investigated the effectiveness of Music-supported Therapy as a therapeutic tool in the rehabilitation of upper extremity motor function after stroke, showing that this therapy is as effective as conventional therapy. Music-supported Therapy can reduce motor impairment and improve the functionality of the upper extremity in subacute and chronic stroke patients. Regarding the time course of motor gains throughout the Music-supported Therapy sessions, improvements in the musical task performance occur rapidly during the first training sessions. However, functional gains and recovery of motor deficits are evidenced at the end of the training program. Interestingly, a second period of Music-supported Therapy leads to a more substantial enhancement of the upper extremity motor function. Improvements in the musical task performance and motor gains promoted by Music-supported Therapy generalise to activities of daily living. Importantly, the enhancement of the upper extremity motor function, the reduction of motor deficits, and the generalisation of motor gains to activities of daily living are maintained three months after finishing the treatment.

The individual's capacity to experience reward from musical activities is related to motor gains in those patients treated with Music-supported Therapy. This means that patients who are more sensitive to experience pleasure from musical activities improve more during Music-supported Therapy, indicating that individualisation of treatments in the patient-centred process of rehabilitation is of much relevance for motor learning.

Apart from the benefits of Music-supported Therapy at the motor level, stroke patients treated with this therapy enhance their language abilities, report less fatigue and negative emotions and improve their quality of life more than those patients treated only with conventional therapy. Therefore, promoting the same amount of motor gains as conventional therapy, Music-supported Therapy is superior in boosting patients' language abilities, enhancing their mood and increasing their quality of life.

The mechanisms that underpin Music-supported Therapy and allow functional recovery are not fully understood. We found that Music-supported Therapy promotes changes in the excitability of the sensorimotor cortex and cortical map reorganisation in subacute stroke patients. However, when compared to conventional therapy, there are no differences between Music-supported Therapy and conventional therapy in the reorganisation of motor regions. Further research on the neural plastic mechanisms associated with this therapy will elucidate how Music-supported Therapy boosts endogenous plasticity and promotes brain reorganisation to achieve functional recovery.

References

References

- Abe, M., Schambra, H., Wassermann, E. M., Luckenbaugh, D., Schweighofer, N., & Cohen, L. G. (2011). Reward improves long-term retention of a motor memory through induction of offline memory gains. *Current Biology*, *21*(7), 557–562. <https://doi.org/10.1016/j.cub.2011.02.030>
- Adams, H. P., Bendixen, B. H., Kappelle, L. J., Biller, J., Love, B. B., Gordon, D. L., & Marsh, E. E. (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, *24*(1), 35–41. <https://doi.org/10.1161/01.STR.24.1.35>
- Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. E. (2006). Reward-Motivated Learning: Mesolimbic Activation Precedes Memory Formation. *Neuron*, *50*(3), 507–517. <https://doi.org/10.1016/j.neuron.2006.03.036>
- Alawieh, A., Tomlinson, S., Adkins, D. A., Kautz, S., & Feng, W. (2017). Preclinical and Clinical Evidence on Ipsilateral Corticospinal Projections: Implication for Motor Recovery. *Translational Stroke Research*, *8*(6), 529–540. <https://doi.org/10.1007/s12975-017-0551-5>
- Albert, S. J., & Kesselring, J. (2012). Neurorehabilitation of stroke. *Journal of Neurology*, *259*(5), 817–832. <https://doi.org/10.1007/s00415-011-6247-y>
- Alford, V. M., Ewen, S., Webb, G. R., Mcginley, J., Brookes, A., & Remedios, L. J. (2015). The use of the International Classification of Functioning, Disability and Health to understand the health and functioning experiences of people with chronic conditions from the person perspective: a systematic review. *Disability and Rehabilitation*, *37*(8), 655–666. <https://doi.org/10.3109/09638288.2014.935875>
- Algurén, B., Fridlund, B., Cieza, A., Sunnerhagen, K. S., & Christensson, L. (2012). Factors associated with health-related quality of life after stroke: A 1-year prospective cohort study. *Neurorehabilitation and Neural Repair*, *26*(3), 266–274. <https://doi.org/10.1177/1545968311414204>
- Alonso, J., Prieto, L., & Antó, J. M. (1995). La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): un instrumento para la medida de los resultados clínicos. *Med Clin (Barc)*, *104*(20), 771–776.
- Altenmüller, E., Marco-Pallares, J., Münte, T. F., & Schneider, S. (2009). Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy. *Annals of the New York Academy of Sciences*, *1169*, 395–405. <https://doi.org/10.1111/j.1749-6632.2009.04580.x>
- Altenmüller, E., & Schlaug, G. (2015). Apollo's gift: new aspects of neurologic music therapy. *Progress in Brain Research*, *217*, 237–252. <https://doi.org/10.1016/bs.pbr.2014.11.029>
- Alves-Pinto, A., Turova, V., Blumenstein, T., & Lampe, R. (2016). The Case for Musical Instrument Training in Cerebral Palsy for Neurorehabilitation. *Neural Plasticity*, *2016*, 1072301. <https://doi.org/10.1155/2016/1072301>
- Amengual, J. L., Rojo, N., Veciana de las Heras, M., Marco-Pallarés, J., Grau-Sánchez, J., Schneider, S., ... Rodríguez-Fornells, A. (2013). Sensorimotor Plasticity after Music-Supported Therapy in Chronic Stroke Patients Revealed by Transcranial Magnetic Stimulation. *PLoS ONE*, *8*(4), e61883. <https://doi.org/10.1371/journal.pone.0061883>
- Amengual, J. L., Valero-Cabré, A., de las Heras, M. V., Rojo, N., Froudast-Walsh, S., Ripollés, P., ... Rodríguez-Fornells, A. (2012). Prognostic value of cortically induced motor evoked activity by TMS in chronic stroke: Caveats from a revealing single clinical case. *BMC Neurology*,

References

- 12(1), 35. <https://doi.org/10.1186/1471-2377-12-35>
- André, J. M., Didier, J. P., & Paysant, J. (2004). "Functional motor amnesia" in stroke (1904) and "learned non-use phenomenon" (1966). *Journal of Rehabilitation Medicine*, 36(3), 138–140. <https://doi.org/10.1080/16501970410026107>
- Aronowski, J., Wagner, K. R., Xi, G., & Zhang, J. H. (2016). Mechanisms of Cerebral Hemorrhage. In J. C. Grotta, G. W. Albers, J. P. Broderick, S. E. Kasner, A. Eng H. Lo, D. Mendelow, ... L. K. Wong (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management* (Sixth Edit, pp. 102–112). Elsevier Inc. <https://doi.org/10.1016/B978-0-323-29544-4.00008-6>
- Arya, K. N., Verma, R., Garg, R. K., Sharma, V. P., Agarwal, M., & Aggarwal, G. G. (2012). Meaningful Task-Specific Training (MTST) for Stroke Rehabilitation: A Randomized Controlled Trial. *Topics in Stroke Rehabilitation*, 19(3), 193–211. <https://doi.org/10.1310/tsr1903-193>
- Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, 26(3), 839–851. <https://doi.org/10.1016/j.neuroimage.2005.02.018>
- Awenowicz, P. W., & Porter, L. L. (2002). Local Application of Dopamine Inhibits Pyramidal Tract Neuron Activity in the Rodent Motor Cortex. *Journal of Neurophysiology*, 88(6), 3439–3451. <https://doi.org/10.1152/jn.00078.2002>
- Ay, H. (2016). Classification of Ischemic Stroke. In J. C. Grotta, G. W. Albers, J. P. Broderick, S. E. Kasner, A. Eng H Lo, D. Mendelow, ... L. K. Wong (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management* (Sixth Edit). Elsevier Inc. <https://doi.org/10.1016/B978-0-323-29544-4.00020-7>
- Bailey, R. R., Klaesner, J. W., & Lang, C. E. (2015). Quantifying Real-World Upper-Limb Activity in Nondisabled Adults and Adults with Chronic Stroke. *Neurorehabilitation and Neural Repair*, 29(10), 969–978. <https://doi.org/10.1177/1545968315583720>
- Baker, S. N. (2011). The primate reticulospinal tract, hand function and functional recovery. *Journal of Physiology*, 589(23), 5603–5612. <https://doi.org/10.1113/jphysiol.2011.215160>
- Bamford, J., Sandercock, P., Dennis, M., Warlow, C., & Burn, J. (1991). Classification and natural history of clinically identifiable subtypes of cerebral infarction. *The Lancet*, 337(8756), 1521–1526. [https://doi.org/10.1016/0140-6736\(91\)93206-0](https://doi.org/10.1016/0140-6736(91)93206-0)
- Bang, D. H., Shin, W. S., & Choi, H. S. (2015). Effects of modified constraint-induced movement therapy combined with trunk restraint in chronic stroke: A double-blinded randomized controlled pilot trial. *NeuroRehabilitation*, 37(1), 131–137. <https://doi.org/10.3233/NRE-151245>
- Bangert, M., Peschel, T., Schlaug, G., Rotte, M., Drescher, D., Hinrichs, H., ... Altenmüller, E. (2006). Shared networks for auditory and motor processing in professional pianists: Evidence from fMRI conjunction. *NeuroImage*, 30(3), 917–926. <https://doi.org/10.1016/j.neuroimage.2005.10.044>
- Barany, D. A., Della-Maggiore, V., Viswanathan, S., Cieslak, M., & Grafton, S. T. (2014). Feature Interactions Enable Decoding of Sensorimotor Transformations for Goal-Directed Movement. *Journal of Neuroscience*, 34(20), 6860–6873. <https://doi.org/10.1523/JNEUROSCI.5173-13.2014>
- Barclay-Goddard, R., & Thalman, L. (2011). Mental practice for treating upper extremity deficits in individuals with hemiparesis after stroke. *Cochrane Database of Systematic Reviews*, (5), CD005950. <https://doi.org/10.1002/14651858.CD005950.pub4>
- Barker-Collo, S., Bennett, D. A., Krishnamurthi, R. V., Parmar, P., Feigin, V. L., Naghavi, M., ... Derrick A, B. (2015). Sex Differences in Stroke Incidence, Prevalence, Mortality and DALYs: Results from the Global Burden of Disease Study 2013. *Neuroepidemiology*, 45(3), 203–214. <https://doi.org/10.1159/000441103>

References

- Baron, J. C., Rougemont, D., Soussaline, F., Bustany, P., Crouzel, C., Bousser, M. G., & Comar, D. (1984). Local interrelationships of cerebral oxygen consumption and glucose utilization in normal subjects and in ischemic stroke patients: A positron tomography study. *Journal of Cerebral Blood Flow and Metabolism*, 4(2), 140–149. <https://doi.org/10.1038/jcbfm.1984.22>
- Barreca, S. R., Gowland, C. K., Stratford, P., Huijbregts, M., Griffiths, J., Torresin, W., ... Masters, L. (2015). Development of the Chedoke Arm and Hand Activity Inventory: Theoretical Constructs, Item Generation, and Selection. *Topics in Stroke Rehabilitation*, 11(4), 31–42. <https://doi.org/10.1310/JU8P-UVK6-68VW-CF3W>
- Barreca, S. R., Stratford, P. W., Lambert, C. L., Masters, L. M., & Streiner, D. L. (2005). Test-retest reliability, validity, and sensitivity of the Chedoke arm and hand activity inventory: a new measure of upper-limb function for survivors of stroke. *Archives of Physical Medicine and Rehabilitation*, 86(8), 1616–1622. <https://doi.org/10.1016/j.apmr.2005.03.017>
- Baumann, S., Koeneke, S., Meyer, M., Lutz, K., & Jäncke, L. (2005). A network for sensory-motor integration: what happens in the auditory cortex during piano playing without acoustic feedback? *Annals of the New York Academy of Sciences*, 1060, 186–188. <https://doi.org/10.1196/annals.1360.038>
- Baumann, S., Koeneke, S., Schmidt, C. F., Meyer, M., Lutz, K., & Jancke, L. (2007). A network for audio-motor coordination in skilled pianists and non-musicians. *Brain Research*, 1161, 65–78. <https://doi.org/10.1016/j.brainres.2007.05.045>
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, 4(6), 561–571. <https://doi.org/10.1001/archpsyc.1961.01710120031004>
- Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., & Ullén, F. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nature Neuroscience*, 8(9), 1148–1150. <https://doi.org/10.1038/nn1516>
- Berner, M. P., & Hoffman, J. (2009). Acquisition of effector-specific and effector-independent components of sequencing skill. *Journal of Motor Behavior*, 41(1), 30–44. <https://doi.org/10.1080/00222895.2009.10125918>
- Bernhardt, J., Borschmann, K., Boyd, L., Carmichael, S. T., Corbett, D., Cramer, S. C., ... Ward, N. (2017). Moving Rehabilitation Research Forward: Developing Consensus Statements for Rehabilitation and Recovery Research. *Neurorehabilitation and Neural Repair*, 31(8), 694–698. <https://doi.org/10.1177/1545968317724290>
- Bernhardt, J., Churilov, L., Ellery, F., Collier, J., Chamberlain, J., Langhorne, P., ... Donnan, G. (2016). Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology*, 86(23), 2138–2145. <https://doi.org/10.1212/WNL.0000000000002459>
- Bernhardt, J., Hayward, K. S., Kwakkel, G., Ward, N. S., Wolf, S. L., Borschmann, K., ... Cramer, S. C. (2017). Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. *Neurorehabilitation and Neural Repair*, 31(9), 793–799. <https://doi.org/10.1177/1545968317732668>
- Berridge, K. C. (2007). The debate over dopamine's role in reward: The case for incentive salience. *Psychopharmacology*, 191(3), 391–431. <https://doi.org/10.1007/s00213-006-0578-x>
- Bickenbach, J. (2012). Ethics, Disability and the International Classification of Functioning, Disability and Health. *American Journal of Physical Medicine & Rehabilitation*, 91, S163–S167. <https://doi.org/10.1097/PHM.0b013e31823d5487>
- Biernaskie, J. (2004). Efficacy of Rehabilitative Experience Declines with Time after Focal

References

- Ischemic Brain Injury. *Journal of Neuroscience*, 24(5), 1245–1254. <https://doi.org/10.1523/JNEUROSCI.3834-03.2004>
- Biernaskie, J., & Corbett, D. (2001). Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *The Journal of Neuroscience*, 21(14), 5272–5280. <https://doi.org/21/14/5272>
- Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., ... Fernandez, M. (2009). How we design feasibility studies. *American Journal of Preventive Medicine*, 36(5), 452–457. <https://doi.org/10.1016/j.amepre.2009.02.002>
- Braun, S., Kleynen, M., van Heel, T., Kruihof, N., Wade, D., & Beurskens, A. (2013). The effects of mental practice in neurological rehabilitation; a systematic review and meta-analysis. *Frontiers in Human Neuroscience*, 7, 390. <https://doi.org/10.3389/fnhum.2013.00390>
- Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial Normalization of Brain Images with Focal Lesions Using Cost Function Masking. *NeuroImage*, 14(2), 486–500. <https://doi.org/10.1006/nimg.2001.0845>
- Brisenden, S. (1986). Independent Living and the Medical Model of Disability. *Disability, Handicap & Society*, 1(2), 173–178. <https://doi.org/10.1080/02674648666780171>
- Brott, T., Jr, H. P. A., Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., ... Walker, M. (1989). Measurements of Acute Cerebral Infarction: a clinical examination scale. *Stroke*, 20(7), 864–870.
- Brust, J. C. M., & Chamorro, A. (2016). Anterior Cerebral Artery Disease. In J. C. Grotta, G. W. Albers, J. P. Broderick, S. E. Kasner, A. Eng H Lo, D. Mendelow, ... L. K. Wong (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management* (Sixth Edit, p. 347–361.e8). Elsevier Inc. <https://doi.org/10.1016/B978-0-323-29544-4.00023-2>
- Buma, F., Kwakkel, G., & Ramsey, N. (2013). Understanding upper limb recovery after stroke. *Restorative Neurology and Neuroscience*, 31(6), 707–722. <https://doi.org/10.3233/RNN-130332>
- Bunketorp-Käll, L., Lundgren-Nilsson, Å., Nilsson, M., & Blomstrand, C. (2017). Multimodal rehabilitation in the late phase after stroke enhances the life situation of informal caregivers. *Topics in Stroke Rehabilitation*, 1–7. <https://doi.org/10.1080/10749357.2017.1413761>
- Bunketorp-Käll, L., Lundgren-Nilsson, Å., Samuelsson, H., Pekny, T., Blomvé, K., Pekna, M., ... Nilsson, M. (2017). Long-Term Improvements after Multimodal Rehabilitation in Late Phase after Stroke. *Stroke*, 48(7), 1916–1924. <https://doi.org/10.1161/STROKEAHA.116.016433>
- Bunketorp Käll, L., Lundgren-Nilsson, Å., Blomstrand, C., Pekna, M., Pekny, M., & Nilsson, M. (2012). The effects of a rhythm and music-based therapy program and therapeutic riding in late recovery phase following stroke: A study protocol for a three-armed randomized controlled trial. *BMC Neurology*, 12, 141. <https://doi.org/10.1186/1471-2377-12-141>
- Byblow, W. D., Stinear, C. M., Barber, P. A., Petoe, M. A., & Ackerley, S. J. (2015). Proportional recovery after stroke depends on corticomotor integrity. *Annals of Neurology*, 78(6), 848–859. <https://doi.org/10.1002/ana.24472>
- Byrnes, M. L., Thickbroom, G. W., Phillips, B. A., Wilson, S. A., & Mastaglia, F. L. (1999). Physiological studies of the corticomotor projection to the hand after subcortical stroke. *Clinical Neurophysiology*, 110(3), 487–498. [https://doi.org/10.1016/S1388-2457\(98\)00044-3](https://doi.org/10.1016/S1388-2457(98)00044-3)
- Calautti, C., Leroy, F., Guincestre, J. Y., & Baron, J. C. (2003). Displacement of primary sensorimotor cortex activation after subcortical stroke: A longitudinal PET study with

References

- clinical correlation. *NeuroImage*, 19(4), 1650–1654. [https://doi.org/10.1016/S1053-8119\(03\)00205-2](https://doi.org/10.1016/S1053-8119(03)00205-2)
- Campo, P., Garrido, M. I., Moran, R. J., Maestú, F., García-Morales, I., Gil-Nagel, A., ... Friston, K. J. (2012). Remote effects of hippocampal sclerosis on effective connectivity during working memory encoding: A case of connectional diaschisis? *Cerebral Cortex*, 22(6), 1225–1236. <https://doi.org/10.1093/cercor/bhr201>
- Carey, L. M., Abbott, D. ., Puce, A., Jackson, G. ., Syngeniotis, A., & Donnan, G. . (2002). Reemergence of activation with poststroke somatosensory recovery: A serial fMRI case study. *Neurology*, 59(5), 749–752. <https://doi.org/10.1212/WNL.59.5.749>
- Carey, L. M., Abbott, D. F., Egan, G. F., O'Keefe, G. J., Jackson, G. D., Bernhardt, J., & Donnan, G. A. (2006). Evolution of brain activation with good and poor motor recovery after stroke. *Neurorehabilitation and Neural Repair*, 20(1), 24–41. <https://doi.org/10.1177/1545968305283053>
- Carey, L., Polatajko, H., Connor, L. ., & Baum, C. M. (2012). Stroke rehabilitation: a learning perspective. In L. Carey (Ed.), *Stroke rehabilitation: insights from neuroscience and imaging*. New York: Oxford University Press.
- Carmichael, S. T. (2006). Cellular and molecular mechanisms of neural repair after stroke: Making waves. *Annals of Neurology*, 59(5), 735–742. <https://doi.org/10.1002/ana.20845>
- Carmichael, S. T., Archibeque, I., Luke, L., Nolan, T., Momiy, J., & Li, S. (2005). Growth-associated gene expression after stroke: Evidence for a growth-promoting region in peri-infarct cortex. *Experimental Neurology*, 193(2), 291–311. <https://doi.org/10.1016/j.expneurol.2005.01.004>
- Carmichael, S. T., & Krakauer, J. W. (2013). The promise of neuro-recovery after stroke: Introduction. *Stroke*, 44(suppl 1), S103. <https://doi.org/10.1161/STROKEAHA.111.000373>
- Carmichael, S. T., Tatsukawa, K., Katsman, D., Tsuyuguchi, N., & Kornblum, H. I. (2004). Evolution of Diaschisis in a Focal Stroke Model. *Stroke*, 35(3), 758–763. <https://doi.org/10.1161/01.STR.0000117235.11156.55>
- Carmichael, S. T., Wei, L., Rovainen, C. M., Woolsey, T. A., Thomas Carmichael, S., Wei, L., ... Woolsey, T. A. (2001). New patterns of intracortical projections after focal cortical stroke. *Neurobiology of Disease*, 8(5), 910–922. <https://doi.org/10.1006/nbdi.2001.0425>
- Carod-Artal, J., Egido, J. A., González, J. L., Varela de Seijas, E., & Seijas, E. V. (2000). Quality of life among stroke survivors evaluated 1 year after stroke: Experience of a stroke unit. *Stroke*, 31(12), 2995–3000. <https://doi.org/10.1161/01.STR.31.12.2995>
- Caroni, P., Donato, F., & Muller, D. (2012). Structural plasticity upon learning: regulation and functions. *Nature Reviews Neuroscience*, 13(7), 478–490. <https://doi.org/10.1038/nrn3258>
- Carr, J. H., & Sheperd, R. . (1987). *Motor relearning programme for stroke* (2nd ed.). London: Heinemann Medical.
- Carr, J. H., & Sheperd, R. . (1990). A motor learning model for the rehabilitation of the movement disabled. In L. Ada & C. Canning (Eds.), *Key issues in neurological physiotherapy*. Oxford: Heinemann Medical.
- Carrera, E., & Tononi, G. (2014). Diaschisis: Past, present, future. *Brain*. Oxford University Press. <https://doi.org/10.1093/brain/awu101>
- Carroll, D. (1965). A quantitative test of upper extremity function. *Journal of Chronic Diseases*, 18(5), 479–491. [https://doi.org/10.1016/0021-9681\(65\)90030-5](https://doi.org/10.1016/0021-9681(65)90030-5)
- Censor, N., Sagi, D., & Cohen, L. G. (2012). Common mechanisms of human perceptual and motor learning. *Nature Reviews Neuroscience*, 13, 658–664. <https://doi.org/10.1038/nrn3315>

References

- Chen, H. M., Chen, C., Hsueh, I. P., Huang, S. I., & Hsieh, C. L. (2009). Test-Retest Reproducibility and Smallest Real With Stroke. *Neurorehabilitation and Neural Repair*, 23(17), 435–440. <https://doi.org/10.1177/1545968308331146>
- Chen, J. L., Rae, C., & Watkins, K. E. (2012). Learning to play a melody: An fMRI study examining the formation of auditory-motor associations. *NeuroImage*, 59(2), 1200–1208. <https://doi.org/10.1016/j.neuroimage.2011.08.012>
- Chiviacowsky, S., & Wulf, G. (2007). Feedback after good trials enhances learning. *Research Quarterly for Exercise and Sport*, 78(2), 40–47. <https://doi.org/10.1080/02701367.2007.10599402>
- Choi, K. D., Lee, H., & Kim, J. S. (2013). Vertigo in brainstem and cerebellar strokes. *Current Opinion in Neurology*, 26(1), 90–95. <https://doi.org/10.1097/WCO.0b013e32835c5edd>
- Chollet, F., Dipiero, V., Wise, R. J. S., Brooks, D. J., Dolan, R. J., & Frackowiak, R. S. J. (1991). The functional anatomy of motor recovery after stroke in humans: A study with positron emission tomography. *Annals of Neurology*, 29(1), 63–71. <https://doi.org/10.1002/ana.410290112>
- Cicinelli, P., Pasqualetti, P., Zaccagnini, M., Traversa, R., Olivefi, M., & Rossini, P. M. (2003). Interhemispheric Asymmetries of Motor Cortex Excitability in the Postacute Stroke Stage: A Paired-Pulse Transcranial Magnetic Stimulation Study. *Stroke*, 34(11), 2653–2658. <https://doi.org/10.1161/01.STR.0000092122.96722.72>
- Cirelli, L. K., Einarson, K. M., & Trainor, L. J. (2014). Interpersonal synchrony increases prosocial behavior in infants. *Developmental Science*, 17(6), 1003–1011. <https://doi.org/10.1111/desc.12193>
- Cirstea, C. M., & Levin, M. F. (2000). Compensatory strategies for reaching in stroke. *Brain*, 123(5), 940–953. <https://doi.org/10.1093/brain/123.5.940>
- Cirstea, C. M., Savage, C. R., Nudo, R. J., Cohen, L. G., Yeh, H. W., Choi, I. Y., ... Brooks, W. M. (2014). Handgrip-related activation in the primary motor cortex relates to underlying neuronal metabolism after stroke. *Neurorehabilitation and Neural Repair*, 28(5), 433–442. <https://doi.org/10.1177/1545968313516868>
- Clarkson, A. N., & Carmichael, S. T. (2009). Cortical excitability and post-stroke recovery. *Biochemical Society Transactions*, 37(6), 1412–1414. <https://doi.org/10.1042/BST0371412>
- Clarkson, A. N., Huang, B. S., MacIsaac, S. E., Mody, I., & Carmichael, S. T. (2010). Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature*, 468(7321), 305–309. <https://doi.org/10.1038/nature09511>
- Classen, J., Liepert, J., Wise, S. P., Hallett, M., Leonardo, G., Baarbé, J., ... Cohen, L. G. (2014). Rapid Plasticity of Human Cortical Movement Representation Induced by Practice Rapid Plasticity of Human Cortical Movement Representation Induced by Practice. *Journal of Neurophysiology*, 79, 1117–1123.
- Conditt, M. A., Gandolfo, F., & Mussa-Ivaldi, F. A. (1997). The motor system does not learn the dynamics of the arm by rote memorization of past experience. *Journal of Neurophysiology*, 78(1), 554–560. <https://doi.org/10.1152/jn.1997.78.1.554>
- Corbetta, D., Sirtori, V., Castellini, G., Moja, L., & Gatti, R. (2015). Constraint-induced movement therapy for upper extremities in people with stroke. *Cochrane Database of Systematic Reviews*, 2017(9), CD004433. <https://doi.org/10.1002/14651858.CD004433.pub3>
- Craciunas, S. C., Brooks, W. M., Nudo, R. J., Popescu, E. A., Choi, I. Y., Lee, P., ... Cirstea, C. M. (2013). Motor and premotor cortices in subcortical stroke: Proton magnetic resonance spectroscopy measures and arm motor impairment. *Neurorehabilitation and Neural Repair*, 27(5), 411–420. <https://doi.org/10.1177/1545968312469835>

References

- Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2014). *Developing and evaluating complex interventions: new guidance*.
- Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M., ... Medical Research Council Guidance. (2008). Developing and evaluating complex interventions: The new Medical Research Council guidance. *BMJ*, *337*, a1655. <https://doi.org/10.1136/bmj.a1655>
- Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of Neurology*, *63*(3), 272–287. <https://doi.org/10.1002/ana.21393>
- Cramer, S. C., & Crafton, K. R. (2006). Somatotopy and movement representation sites following cortical stroke. *Experimental Brain Research*, *168*(1–2), 25–32. <https://doi.org/10.1007/s00221-005-0082-2>
- Cramer, S. C., Finklestein, S. P., Schaechter, J. D., Bush, G., & Rosen, B. R. (1999). Activation of Distinct Motor Cortex Regions During Ipsilateral and Contralateral Finger Movements. *Journal of Neurophysiology*, *81*(1), 383–387. <https://doi.org/10.1152/jn.1999.81.1.383>
- Cramer, S. C., Nelles, G., Benson, R. R., Kaplan, J. D., Parker, R. A., Kwong, K. K., ... Rosen, B. R. (1997). A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*, *28*(12), 2518–2527. <https://doi.org/10.1161/01.STR.28.12.2518>
- Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., ... Vinogradov, S. (2011). Harnessing neuroplasticity for clinical applications. *Brain*, *134*(6), 1591–1609. <https://doi.org/10.1093/brain/awr039>
- Crocker, T., Forster, A., Young, J., Brown, L., Ozer, S., Smith, J., ... Greenwood, D. C. (2013). Physical rehabilitation for older people in long-term care. *Cochrane Database of Systematic Reviews*, (2), CD004294. <https://doi.org/10.1002/14651858.CD004294.pub3>
- Cunningham, D. A., Machado, A., Yue, G. H., Carey, J. R., & Plow, E. B. (2013). Functional somatotopy revealed across multiple cortical regions using a model of complex motor task. *Brain Research*, *1531*, 25–36. <https://doi.org/10.1016/j.brainres.2013.07.050>
- D'Ausilio, A., Brunetti, R., Delogu, F., Santonico, C., & Belardinelli, M. O. (2010). How and when auditory action effects impair motor performance. *Experimental Brain Research*, *201*(2), 323–330. <https://doi.org/10.1007/s00221-009-2044-6>
- Dalise, S., Ambrosio, F., & Modò, M. (2014). Adaptive plasticity and recovery in preclinical models of stroke. *Archives Italiennes de Biologie*, *152*(4), 190–215. <https://doi.org/10.12871/00039829201442>
- Dancause, N., & Nudo, R. J. (2011). Shaping plasticity to enhance recovery after injury. *Progress in Brain Research*, *192*, 273–295. <https://doi.org/10.1016/B978-0-444-53355-5.00015-4>
- Daniel, K., Wolfe, C. D. A. A., Busch, M. A., & Mckeivitt, C. (2009). What are the social consequences of stroke for working-aged adults?: a systematic review. *Stroke*, *40*(6), 431–441. <https://doi.org/10.1161/STROKEAHA.108.534487>
- Dayan, E., & Cohen, L. G. (2011). Neuroplasticity subserving motor skill learning. *Neuron*, *72*(3), 443–454. <https://doi.org/10.1016/j.neuron.2011.10.008>
- De Wit, L., Putman, K., Dejaeger, E., Baert, I., Berman, P., Bogaerts, K., ... De Weerd, W. (2005). Use of time by stroke patients: A comparison of four European rehabilitation centers. *Stroke*, *36*(9), 1977–1983. <https://doi.org/10.1161/01.STR.0000177871.59003.e3>
- Dehlendorff, C., Andersen, K. K., & Olsen, T. S. (2015). Sex Disparities in Stroke: Women Have More Severe Strokes but Better Survival Than Men. *Journal of the American Heart Association*, *4*(7). <https://doi.org/10.1161/JAHA.115.001967>
- DeJong, G., Horn, S. D., Conroy, B., Nichols, D., & Heaton, E. B. (2005). Opening the black box of poststroke rehabilitation: Stroke rehabilitation patients, processes, and outcomes. *Archives*

References

- of Physical Medicine and Rehabilitation*, 86(12 SUPPL.), 1–7.
[https://doi.org/10.1016/S0966-6532\(05\)80005-8](https://doi.org/10.1016/S0966-6532(05)80005-8)
- Di Piero, V., Chollet, F., Dolan, R. J., Thomas, D. J., & Frackowiak, R. (1990). The functional nature of cerebellar diaschisis. *Stroke*, 21(9), 1365–1369.
<https://doi.org/10.1161/01.STR.21.9.1365>
- Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., ... Di Lazzaro, V. (2014). Modulation of brain plasticity in stroke: A novel model for neurorehabilitation. *Nature Reviews Neurology*. <https://doi.org/10.1038/nrneurol.2014.162>
- Dobkin, B. H. (2004). Strategies for stroke rehabilitation. *Lancet Neurology*, 3(9), 528–536.
[https://doi.org/10.1016/S1474-4422\(04\)00851-8](https://doi.org/10.1016/S1474-4422(04)00851-8)
- Doyon, J., & Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Current Opinion in Neurobiology*, 15(2), 161–167.
<https://doi.org/10.1016/j.conb.2005.03.004>
- Draganski, B., & May, A. (2008). Training-induced structural changes in the adult human brain. *Behavioural Brain Research*, 192(1), 137–142. <https://doi.org/10.1016/j.bbr.2008.02.015>
- Draganski, Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Changes in grey matter induced by training. *Nature*, 427(6972), 311–312.
<https://doi.org/10.1038/427311a>
- Duff, M., Chen, Y., Cheng, L., Liu, S. M., Blake, P., Wolf, S. L., & Rikakis, T. (2013). Adaptive mixed reality rehabilitation improves quality of reaching movements more than traditional reaching therapy following stroke. *Neurorehabilitation and Neural Repair*, 27(4), 306–315.
<https://doi.org/10.1177/1545968312465195>
- Duque, J., Hummel, F., Celnik, P., Murase, N., Mazzocchio, R., & Cohen, L. G. (2005). Transcallosal inhibition in chronic subcortical stroke. *NeuroImage*, 28(4), 940–946.
<https://doi.org/10.1016/j.neuroimage.2005.06.033>
- Dyrlund, A. K., & Wininger, S. R. (2008). The effects of music preference and exercise intensity on psychological variables. *Journal of Music Therapy*, 45(2), 114–134.
<https://doi.org/10.1093/jmt/45.2.114>
- Eitam, B., Kennedy, P. M., & Higgins, E. T. (2013). Motivation from control. *Experimental Brain Research*, 229(3), 475–484. <https://doi.org/10.1007/s00221-012-3370-7>
- Eldridge, S., Spencer, A., Cryer, C., Parsons, S., Underwood, M., & Feder, G. (2005). Why modelling a complex intervention is an important precursor to trial design: lessons from studying an intervention to reduce falls-related injuries in older people. *Journal of Health Services Research & Policy*, 10(3), 133–142. <https://doi.org/10.1258/1355819054338942>
- Eraifej, J., Clark, W., France, B., Desando, S., & Moore, D. (2017). Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: A systematic review and meta-analysis. *Systematic Reviews*, 6(1), 40.
<https://doi.org/10.1186/s13643-017-0435-5>
- Fedorov, A., Beichel, R., Kalpathy-Cramer, J., Finet, J., Fillion-Robbin, J.-C., Pujol, S., ... Kikinis, R. (2012). 3D slicers as an image computing platform for thw quantitative imaging network. *Magnetic Resonance Imaging*, 30(9), 1323–1341.
<https://doi.org/10.1016/j.mri.2012.05.001.3D>
- Feeley, N., Cossette, S., Côté, J., Héon, M., Stremler, R., Martorella, G., & Purden, M. (2009). The importance of piloting an RCT intervention. *Canadian Journal of Nursing Research*, 41(2), 84–99.
- Feigin, V. L., Mensah, G. A., Norrving, B., Murray, C. J. L., & Roth, G. A. (2015). Atlas of the Global Burden of Stroke (1990-2013): The GBD 2013 Study. *Neuroepidemiology*, 45(3), 230–236.

References

- <https://doi.org/10.1159/000441106>
- Feigin, V. L., Norrving, B., & Mensah, G. A. (2017). Global Burden of Stroke. *Circulation Research*, *120*(3), 439–448. <https://doi.org/10.1161/CIRCRESAHA.116.308413>
- Finger, S., Koehler, P. J., & Jagella, C. (2004). The Monakow Concept of Diaschisis: Origins and Perspectives. *Archives of Neurology*, *61*(2), 283–288. <https://doi.org/10.1001/archneur.61.2.283>
- Flynn, D., Ford, G. A., Rodgers, H., Price, C., Steen, N., & Thomson, R. G. (2014). A time series evaluation of the FAST national stroke awareness campaign in England. *PLoS ONE*, *9*(8), e104289. <https://doi.org/10.1371/journal.pone.0104289>
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Fonarow, G. C., Smith, E. E., Saver, J. L., Reeves, M. J., Hernandez, A. F., Peterson, E. D., ... Schwamm, L. H. (2011). Improving door-to-needle times in acute ischemic stroke: The design and rationale for the American Heart Association/American Stroke Association’s target: Stroke initiative. *Stroke*, *42*(10), 2983–2989. <https://doi.org/10.1161/STROKEAHA.111.621342>
- Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience*, *16*(3), 159–172. <https://doi.org/10.1038/nrn3901>
- Foulon, C., Cerliani, L., Kinkingnéhun, S., Levy, R., Rosso, C., Urbanski, M., ... Thiebaut de Schotten, M. (2018). Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. *GigaScience*, *7*(3). <https://doi.org/10.1093/gigascience/giy004>
- François, C., Grau-Sánchez, J., Duarte, E., & Rodriguez-Fornells, A. (2015). Musical training as an alternative and effective method for neuro-education and neuro-rehabilitation. *Frontiers in Psychology*, *6*(APR), 1–15. <https://doi.org/10.3389/fpsyg.2015.00475>
- Friedman, L. M., Furberg, C. D., DeMets, D., Reboussin, D. M., & Granger, C. D. (2015). *Fundamentals of Clinical Trials* (5th ed.). Springer International Publishing.
- Friedman, N., Chan, V., Reinkensmeyer, A. N., Beroukhim, A., Zambrano, G. J., Bachman, M., & Reinkensmeyer, D. J. (2014). Retraining and assessing hand movement after stroke using the MusicGlove: Comparison with conventional hand therapy and isometric grip training. *Journal of NeuroEngineering and Rehabilitation*, *11*(1), 76. <https://doi.org/10.1186/1743-0003-11-76>
- Friston, K., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C., Frackowiak, R. S., & Turner, R. (1995). Analysis of fMRI Time-Series Revisited. *NeuroImage*, *2*(1), 45–53. <https://doi.org/10.1006/nimg.1995.1007>
- Fu, M., Yu, X., Lu, J., & Zuo, Y. (2012). Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. *Nature*, *483*(7387), 92–96. <https://doi.org/10.1038/nature10844>
- Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient. A method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine*, *7*(1), 13–31.
- Furuya, S., & Soechting, J. F. (2010). Role of auditory feedback in the control of successive keystrokes during piano playing. *Experimental Brain Research*, *204*(2), 223–237. <https://doi.org/10.1007/s00221-010-2307-2>
- Galea, J. M., Mallia, E., Rothwell, J., & Diedrichsen, J. (2015). The dissociable effects of punishment and reward on motor learning. *Nature Neuroscience*, *18*(4), 597–602. <https://doi.org/10.1038/nn.3956>

References

- Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *Journal of Neuroscience*, *23*(27), 9240–9245.
- GBD 2016 Causes of Death Collaborators. (2017). Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1151–1210. [https://doi.org/10.1016/S0140-6736\(17\)32152-9](https://doi.org/10.1016/S0140-6736(17)32152-9)
- GBD 2016 DALYs and HALE Collaborators. (2017). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1260–1344. [https://doi.org/10.1016/S0140-6736\(17\)32130-X](https://doi.org/10.1016/S0140-6736(17)32130-X)
- GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1211–1259. [https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/10.1016/S0140-6736(17)32154-2)
- Ghez, C., Gordon, J., & Ghilardi, M. F. (1995). Impairments of reaching movements in patients without proprioception. II. Effects of visual information on accuracy. *Journal of Neurophysiology*, *73*(1), 361–372. <https://doi.org/10.1152/jn.1995.73.1.361>
- Ginsberg, M. D., Castella, Y., Dietrich, W. D., Watson, B. D., & Busto, R. (1989). Acute thrombotic infarction suppresses metabolic activation of ipsilateral somatosensory cortex: Evidence for functional diaschisis. *Journal of Cerebral Blood Flow and Metabolism*, *9*(3), 329–341. <https://doi.org/10.1038/jcbfm.1989.51>
- Glasziou, P., Meats, E., Heneghan, C., & Shepperd, S. (2008). What is missing from descriptions of treatment in trials and reviews? *BMJ*, *336*(7659), 1472–1474. <https://doi.org/10.1136/bmj.39590.732037.47>
- Glees, P., & Cole, J. (1949). The reappearance of coordinated movements of the hand after lesions in the hand area of the motor cortex of the rhesus monkey. *Journal of Physiology*, *108*(1), Proc, 33.
- Grafton, S. T., Hazeltine, E., & Ivry, R. B. (2002). Motor sequence learning with the nondominant left hand. A PET functional imaging study. *Experimental Brain Research*, *146*(3), 369–378. <https://doi.org/10.1007/s00221-002-1181-y>
- Grau-Sánchez, J., Amengual, J. L., Rojo, N., Veciana de Las Heras, M., Montero, J., Rubio, F., ... Rodríguez-Fornells, A. (2013). Plasticity in the sensorimotor cortex induced by Music-supported therapy in stroke patients: a TMS study. *Frontiers in Human Neuroscience*, *7*, 494. <https://doi.org/10.3389/fnhum.2013.00494>
- Grau-Sánchez, J., Duarte, E., Ramos-Escobar, N., Sierpowska, J., Rueda, N., Redón, S., ... Rodríguez-Fornells, A. (2018). Music-supported therapy in the rehabilitation of subacute stroke patients: a randomized controlled trial. *Annals of the New York Academy of Sciences*, *1423*(1), 318–328. <https://doi.org/10.1111/nyas.13590>
- Grau-Sánchez, J., Ramos, N., Duarte, E., Särkämö, T., & Rodríguez-Fornells, A. (2017). Time course of motor gains induced by music-supported therapy after stroke: An exploratory case study. *Neuropsychology*, *31*(6), 624–635. <https://doi.org/10.1037/neu0000355>
- Grefkes, C., Nowak, D. A., Eickhoff, S. B., Dafotakis, M., Küst, J., Karbe, H., & Fink, G. R. (2008). Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Annals of Neurology*, *63*(2), 236–246. <https://doi.org/10.1002/ana.21228>
- Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., ... Siebner, H. R. (2012). A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN

References

- committee. *Clinical Neurophysiology*, 123(5), 858–882.
<https://doi.org/10.1016/j.clinph.2012.01.010>
- Gruber, M. J., Gelman, B. D., & Ranganath, C. (2014). States of Curiosity Modulate Hippocampus-Dependent Learning via the Dopaminergic Circuit. *Neuron*, 84(2), 486–496.
<https://doi.org/10.1016/j.neuron.2014.08.060>
- Guerrero, N., Turry, A., Geller, D., & Raghavan, P. (2014). From historic to contemporary: Nordoff-Robbins Music Therapy in collaborative interdisciplinary rehabilitation. *Music Therapy Perspectives*, 32(1), 38–46. <https://doi.org/10.1093/mtp/miu014>
- Guo, C. C., Ke, M. C., & Raymond, J. L. (2014). Cerebellar Encoding of Multiple Candidate Error Cues in the Service of Motor Learning. *Journal of Neuroscience*, 34(30), 9880–9890.
<https://doi.org/10.1523/JNEUROSCI.5114-13.2014>
- Haast, R., Gustafson, D., & Kiliaan, A. (2012). Sex differences in stroke. *Journal of Cerebral Blood Flow & Metabolism*, 32(12), 2100–2107. <https://doi.org/10.1038/jcbfm.2012.141>
- Hacke, W., Kaste, M., Bluhmki, E., Brozman, M., Dávalos, A., Guidetti, D., ... Toni, D. (2008). Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. *New England Journal of Medicine*, 359(13), 1317–1329. <https://doi.org/10.1056/NEJMoa0804656>
- Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron*, 55(2), 187–199.
<https://doi.org/10.1016/j.neuron.2007.06.026>
- Harris, & Eng, J. J. (2007). Paretic upper-limb strength best explains arm activity in people with stroke. *Physical Therapy*, 87(1), 88–97. <https://doi.org/10.2522/ptj.20060065>
- Harris, J. E., & Hebert, A. (2015). Utilization of motor imagery in upper limb rehabilitation: A systematic scoping review. *Clinical Rehabilitation*, 29(11), 1092–1107.
<https://doi.org/10.1177/0269215514566248>
- Hatano, S. (1976). Experience from a multicentre stroke register: a preliminary report. *Bulletin of the World Health Organization*, 54(5), 541–553.
- Hatem, S. M., Saussez, G., della Faille, M., Prist, V., Zhang, X., Dispa, D., & Bleyenheuft, Y. (2016). Rehabilitation of Motor Function after Stroke: A Multiple Systematic Review Focused on Techniques to Stimulate Upper Extremity Recovery. *Frontiers in Human Neuroscience*, 10, 442. <https://doi.org/10.3389/fnhum.2016.00442>
- Hauelsen, J., & Knösche, T. R. (2001). Involuntary Motor Activity in Pianists Evoked by Music Perception. *Journal of Cognitive Neuroscience*, 13(6), 786–792.
<https://doi.org/10.1162/08989290152541449>
- Helmer, R. J. N., Farrow, D., Ball, K., Phillips, E., Farouil, A., & Blanchonette, I. (2011). A pilot evaluation of an electronic textile for lower limb monitoring and interactive biofeedback. *Procedia Engineering*, 13(3), 513–518. <https://doi.org/10.1016/j.proeng.2011.05.123>
- Herholz, S. C. C., & Zatorre, R. J. J. (2012). Musical Training as a Framework for Brain Plasticity: Behavior, Function, and Structure. *Neuron*, 76(3), 486–502.
<https://doi.org/10.1016/j.neuron.2012.10.011>
- Herrojo Ruiz, M., Brücke, C., Nikulin, V. V., Schneider, G.-H., & Kühn, A. A. (2014). Beta-band amplitude oscillations in the human internal globus pallidus support the encoding of sequence boundaries during initial sensorimotor sequence learning. *NeuroImage*, 85, 779–793. <https://doi.org/10.1016/j.neuroimage.2013.05.085>
- Hickok, G., Buchsbaum, B., Humphries, C., & Muftuler, T. (2003). Auditory-motor interaction revealed by fMRI: Speech, music, and working memory in area Spt. *Journal of Cognitive Neuroscience*, 15(5), 673–682. <https://doi.org/10.1162/089892903322307393>
- Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding

References

- aspects of the functional anatomy of language. *Cognition*, 92(1–2), 67–99. <https://doi.org/10.1016/j.cognition.2003.10.011>
- Hicks, A. U., Hewlett, K., Windle, V., Chernenko, G., Ploughman, M., Jolkkonen, J., ... Corbett, D. (2007). Enriched environment enhances transplanted subventricular zone stem cell migration and functional recovery after stroke. *Neuroscience*, 146(1), 31–40. <https://doi.org/10.1016/j.neuroscience.2007.01.020>
- Hillier, S., & Inglis-Jassiem, G. (2010). Rehabilitation for community-dwelling people with stroke: Home or centre based? A systematic review. *International Journal of Stroke*, 5(3), 178–186. <https://doi.org/10.1111/j.1747-4949.2010.00427.x>
- Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., ... Michie, S. (2014). Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, 348. <https://doi.org/10.1136/bmj.g1687>
- Hooyman, A., Wulf, G., & Lewthwaite, R. (2014). Impacts of autonomy-supportive versus controlling instructional language on motor learning. *Human Movement Science*, 36, 190–198. <https://doi.org/10.1016/j.humov.2014.04.005>
- Hosp, J. A., & Luft, A. R. (2013). Dopaminergic Meso-Cortical Projections to M1: Role in Motor Learning and Motor Cortex Plasticity. *Frontiers in Neurology*, 4, 145. <https://doi.org/10.3389/fneur.2013.00145>
- Hosp, J. A., Pekanovic, A., Rioult-Pedotti, M. S., & Luft, A. R. (2011). Dopaminergic Projections from Midbrain to Primary Motor Cortex Mediate Motor Skill Learning. *Journal of Neuroscience*, 31(7), 2481–2487. <https://doi.org/10.1523/JNEUROSCI.5411-10.2011>
- Hove, M. J., & Risen, J. L. (2009). It's All in the Timing: Interpersonal Synchrony Increases Affiliation. *Social Cognition*, 27(6), 949–960. <https://doi.org/10.1521/soco.2009.27.6.949>
- Howard, V. J. (2013). Reasons underlying racial differences in stroke incidence and mortality. *Stroke*, 44(601), 126–128. <https://doi.org/10.1161/STROKEAHA.111.000691>
- Hubbard, I. J., Carey, L. M., Budd, T. W., Levi, C., McElduff, P., Hudson, S., ... Parsons, M. W. (2015). A Randomized Controlled Trial of the Effect of Early Upper-Limb Training on Stroke Recovery and Brain Activation. *Neurorehabilitation and Neural Repair*, 29(8), 703–713. <https://doi.org/10.1177/1545968314562647>
- Hulley, S., Cummings, S., Browner, W., Grady, D., & Newman, T. (2013). *Designing Clinical Research* (Fourth). Philadelphia: Lippincott Williams & Wilkins.
- Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., & Schlaug, G. (2009). Musical training shapes structural brain development. *Journal of Neuroscience*, 29(10), 3019–3025. <https://doi.org/10.1523/JNEUROSCI.5118-08.2009>
- Hylin, M. J., Kerr, A. L., & Holden, R. (2017). Understanding the mechanisms of recovery and/or compensation following injury. *Neural Plasticity*, 2017, 7125057. <https://doi.org/10.1155/2017/7125057>
- Inman, C. S., James, G. A., Hamann, S., Rajendra, J. K., Pagnoni, G., & Butler, A. J. (2012). Altered resting-state effective connectivity of fronto-parietal motor control systems on the primary motor network following stroke. *NeuroImage*, 59(1), 227–237. <https://doi.org/10.1016/j.neuroimage.2011.07.083>
- Institute for Health Metrics and Evaluation. (2018). Global Health Data Exchange. Retrieved November 29, 2017, from <http://ghdx.healthdata.org>
- Iwakabe, S., & Gazzola, N. (2009). From single-case studies to practice-based knowledge: Aggregating and synthesizing case studies. *Psychotherapy Research*, 19(4–5), 601–611. <https://doi.org/10.1080/10503300802688494>

References

- Jaillard, A., Martin, C. D., Garambois, K., Lebas, J. F., Hommel, M., François Lebas, J., ... Hommel, M. (2005). Vicarious function within the human primary motor cortex? A longitudinal fMRI stroke study. *Brain*, *128*(5), 1122–1138. <https://doi.org/10.1093/brain/awh456>
- Janssen, H., Ada, L., Bernhardt, J., McElduff, P., Pollack, M., Nilsson, M., & Spratt, N. J. (2014). An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomized controlled trial. *Disability and Rehabilitation*, *36*(3), 255–262. <https://doi.org/10.3109/09638288.2013.788218>
- Janssen, H., Bernhardt, J., Collier, J. M., Sena, E. S., McElduff, P., Attia, J., ... Spratt, N. J. (2010). An enriched environment improves sensorimotor function post-ischemic stroke. *Neurorehabilitation and Neural Repair*, *24*(9), 802–813. <https://doi.org/10.1177/1545968310372092>
- Jauch, E. C., Saver, J. L., Adams, H. P., Bruno, A., Connors, J. J. B. B., Demaerschalk, B. M., ... Yonas, H. (2013). Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *44*(3), 870–947. <https://doi.org/10.1161/STR.0b013e318284056a>
- Jin, X., & Costa, R. M. (2015). Shaping action sequences in basal ganglia circuits. *Current Opinion in Neurobiology*, *33*, 188–196. <https://doi.org/10.1016/j.conb.2015.06.011>
- Johansen-Berg, H. (2012). The future of functionally-related structural change assessment. *NeuroImage*, *62*(2), 1293–1298. <https://doi.org/10.1016/j.neuroimage.2011.10.073>
- Johansen-Berg, H., Dawes, H., Guy, C., Smith, S. M., Wade, D. T., & Matthews, P. M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*, *125*(12), 2731–2742. <https://doi.org/10.1093/brain/awg289>
- Johansen-Berg, H., Rushworth, M. F. S., Bogdanovic, M. D., Kischka, U., Wimalaratna, S., & Matthews, P. M. (2002). The role of ipsilateral premotor cortex in hand movement after stroke. *Proceedings of the National Academy of Sciences*, *99*(22), 14518–14523. <https://doi.org/10.1073/pnas.222536799>
- Johansson, B. B. (1996). Functional outcome in rats transferred to an enriched environment 15 days after focal brain ischemia. *Stroke*, *27*(2), 324–326. <https://doi.org/10.1161/01.STR.27.2.324>
- Johansson, B. B., & Ohlsson, A. L. (1996). Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Experimental Neurology*, *139*(2), 322–327. <https://doi.org/10.1006/exnr.1996.0106>
- Jones, T. A. (2017). Motor compensation and its effects on neural reorganization after stroke. *Nature Reviews Neuroscience*, *18*(5), 267–280. <https://doi.org/10.1038/nrn.2017.26>
- Jourden, F., Bandura, A., & Banfield, J. (1991). The impact of conceptions of ability on self-regulatory factors and motor skill acquisition. *Journal of Sport and Exercise Psychology*, *8*(3), 213–226. <https://doi.org/10.1123/jsep.13.3.213>
- Kami, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*, *377*(6545), 155–158. <https://doi.org/10.1038/377155a0>
- Karl, A., Birbaumer, N., Lutzenberger, W., Cohen, L. G., & Flor, H. (2001). Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. *The Journal of Neuroscience*, *21*(10), 3609–3618. <https://doi.org/10.1523/JNEUROSCI.2110-01.2001>
- Karni, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*, *377*(6545), 155–158. <https://doi.org/10.1038/377155a0>

References

- Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 95(3), 861–868. <https://doi.org/10.1073/PNAS.95.3.861>
- Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Systematic Reviews*, 6(1), 259. <https://doi.org/10.1186/s13643-017-0632-2>
- Kim, A. (2014). Evaluation and prevention of cardioembolic stroke. *Continuum: Lifelong Learning in Neurology*, 20(2), 309–322. <https://doi.org/10.1212/01.CON.0000446103.82420.2d>
- Kim, J. S. (2016). Posterior Cerebral Artery Disease. In J. P. Broderick, S. E. Kasner, A. Eng H Lo, D. Mendelow, R. L. Sacco, & L. K. Wong (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management* (Sixth Edit, p. 393–412.e5). Elsevier Inc. <https://doi.org/10.1016/B978-0-323-29544-4.00025-6>
- Kim, J. S., & Caplan, L. R. (2016). Vertebrobasilar Disease. In J. C. Grotta, G. W. Albers, J. P. Broderick, S. E. Kasner, A. Eng H Lo, D. Mendelow, ... L. K. Wong (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management* (Fifth Edit, pp. 413–448). Elsevier Inc. <https://doi.org/10.1016/B978-0-323-29544-4.00026-8>
- Kitago, T., & Krakauer, J. W. (2013). Motor learning principles for neurorehabilitation. In M. P. Barnes & D. C. Good (Eds.), *Handbook of Clinical Neurology* (1st ed., Vol. 110, pp. 93–103). Elsevier B.V. <https://doi.org/10.1016/B978-0-444-52901-5.00008-3>
- Kobayashi, M., & Pascual-Leone, A. (2003). Transcranial magnetic stimulation in neurology. *Lancet Neurology*, 2(3), 145–156. [https://doi.org/10.1016/S1474-4422\(03\)00321-1](https://doi.org/10.1016/S1474-4422(03)00321-1)
- Kolb, B., & Whishaw, I. Q. (1998). Brain Plasticity and behavior. *Annual Review of Psychology*, 49(1), 43–64. <https://doi.org/10.1146/annurev.psych.49.1.43>
- Komitova, M., Mattsson, B., Johansson, B. B., & Eriksson, P. S. (2005). Enriched environment increases neural stem/progenitor cell proliferation and neurogenesis in the subventricular zone of stroke-lesioned adult rats. *Stroke*, 36(6), 1278–1282. <https://doi.org/10.1161/01.STR.0000166197.94147.59>
- Kovacs, A. J., Mühlbauer, T., & Shea, C. H. (2009). The coding and effector transfer of movement sequences. *Journal of Experimental Psychology: Human Perception and Performance*, 35(2), 390–407. <https://doi.org/10.1037/a0012733>
- Koziol, L. F., Budding, D., Andreasen, N., D'Arrigo, S., Bulgheroni, S., Imamizu, H., ... Yamazaki, T. (2014). Consensus Paper: The Cerebellum's Role in Movement and Cognition. *The Cerebellum*, 13(1), 151–177. <https://doi.org/10.1007/s12311-013-0511-x>
- Krakauer, J. W. (2006). Motor learning: its relevance to stroke recovery and neurorehabilitation. *Current Opinion in Neurology*, 19(1), 84–90. <https://doi.org/10.1097/01.wco.0000200544.29915.cc>
- Krakauer, J. W., Carmichael, S. T., Corbett, D., & Wittenberg, G. F. (2012). Getting neurorehabilitation right: What can be learned from animal models? *Neurorehabilitation and Neural Repair*, 26(8), 923–931. <https://doi.org/10.1177/1545968312440745>
- Krakauer, J. W., Ghilardi, M. F., & Ghez, C. (1999). Independent learning of internal models for kinematic and dynamic control of reaching. *Nature Neuroscience*, 2(11), 1026–1031. <https://doi.org/10.1038/14826>
- Krakauer, J. W., & Marshall, R. S. (2015). The proportional recovery rule for stroke revisited. *Annals of Neurology*, 78(6), 845–847. <https://doi.org/10.1002/ana.24537>
- Krishnamurthi, R. V., Feigin, V. L., Forouzanfar, M. H., Mensah, G. A., Connor, M., Bennett, D. A., ...

References

- Murray, C. (2013). Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *The Lancet Global Health*, 1(5), e259-81. [https://doi.org/10.1016/S2214-109X\(13\)70089-5](https://doi.org/10.1016/S2214-109X(13)70089-5)
- Kwakkel, G., Kollen, B., & Lindeman, E. (2004). Understanding the pattern of functional recovery after stroke: facts and theories. *Restorative Neurology and Neuroscience*, 22(3-5), 281-299. <https://doi.org/10.1177/1545968308317972>
- Kwakkel, G., Veerbeek, J. M., van Wegen, E. E. H., & Wolf, S. L. (2015). Constraint-induced movement therapy after stroke. *The Lancet Neurology*, 14(2), 224-234. [https://doi.org/10.1016/S1474-4422\(14\)70160-7](https://doi.org/10.1016/S1474-4422(14)70160-7)
- Lage, G. M., Ugrinowitsch, H., Apolinário-Souza, T., Vieira, M. M., Albuquerque, M. R., & Benda, R. N. (2015). Repetition and variation in motor practice: A review of neural correlates. *Neuroscience and Biobehavioral Reviews*, 57, 132-141. <https://doi.org/10.1016/j.neubiorev.2015.08.012>
- Lahav, A., Saltzman, E., & Schlaug, G. (2007). Action Representation of Sound: Audiomotor Recognition Network While Listening to Newly Acquired Actions. *Journal of Neuroscience*, 27(2), 308-314. <https://doi.org/10.1523/JNEUROSCI.4822-06.2007>
- Lampe, R., Thienel, A., Mitternacht, J., Blumenstein, T., Turova, V., & Alves-Pinto, A. (2015). Piano training in youths with hand motor impairments after damage to the developing brain. *Neuropsychiatric Disease and Treatment*, 11, 1929-1938. <https://doi.org/10.2147/NDT.S84090>
- Lang, C. E., Edwards, D. F., Birkenmeier, R. L., & Dromerick, A. W. (2008). Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Archives of Physical Medicine and Rehabilitation*, 89(9), 1693-1700. <https://doi.org/10.1016/j.apmr.2008.02.022>
- Langhorne, P., Baylan, S., & Early Supported Discharge Trialists. (2017). Early supported discharge services for people with acute stroke. *Cochrane Database of Systematic Reviews*, 7, CD000443. <https://doi.org/10.1002/14651858.CD000443.pub4>
- Langhorne, P., Bernhardt, J., & Kwakkel, G. (2011). Stroke rehabilitation. *The Lancet*, 377, 1693-1702. [https://doi.org/10.1016/S0140-6736\(11\)60325-5](https://doi.org/10.1016/S0140-6736(11)60325-5)
- Langhorne, P., O'Williams, B., Gilchrist, W., & Howie, K. (1993). Do stroke units save lives? *The Lancet*, 342(8868), 395-398. [https://doi.org/10.1016/0140-6736\(93\)92813-9](https://doi.org/10.1016/0140-6736(93)92813-9)
- Lansberg, M. G., Bluhmki, E., & Thijs, V. N. (2009). Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: A metaanalysis. *Stroke*, 40(7), 2438-2441. <https://doi.org/10.1161/STROKEAHA.109.552547>
- Lappe, C., Herholz, S. C., Trainor, L. J., & Pantev, C. (2008). Cortical plasticity induced by short-term unimodal and multimodal musical training. *Journal of Neuroscience*, 28(39), 9632-9639. <https://doi.org/10.1523/JNEUROSCI.2254-08.2008>
- Larrue, V., Von Kummer, R., Müller, A., & Bluhmki, E. (2001). Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: A secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke*, 32(2), 438-441. <https://doi.org/10.1161/01.STR.32.2.438>
- Laukka, P. (2007). Uses of music and psychological well-being among the elderly. *Journal of Happiness Studies*, 8(2), 215-241. <https://doi.org/10.1007/s10902-006-9024-3>
- Laver, K. E., Lange, B., George, S., Deutsch, J. E., Saposnik, G., & Crotty, M. (2017). Virtual reality for stroke rehabilitation. *Cochrane Database of Systematic Reviews*, 2017(11), CD008349. <https://doi.org/10.1002/14651858.CD008349.pub4>
- Lee, Kim, M. Y., Park, J.-H., & Park, H. Y. (2017). Comparison of the effects of bilateral and

References

- unilateral training after stroke: A meta-analysis. *NeuroRehabilitation*, 40(3), 1–13. <https://doi.org/10.3233/NRE-161418>
- Levin, M. F., Kleim, J. A., & Wolf, S. L. (2009). What Do Motor “Recovery” and “Compensation” Mean in Patients Following Stroke? *Neurorehabilitation and Neural Repair*, 23(4), 313–319. <https://doi.org/10.1177/1545968308328727>
- Levin, M. F., Michaelsen, S. M., Cirstea, C. M., & Roby-Brami, A. (2002). Use of the trunk for reaching targets placed within and beyond the reach in adult hemiparesis. *Experimental Brain Research*, 143(2), 171–180. <https://doi.org/10.1007/s00221-001-0976-6>
- Lewthwaite, R., Chiviawsky, S., Drews, R., & Wulf, G. (2015). Choose to move: The motivational impact of autonomy support on motor learning. *Psychonomic Bulletin and Review*, 22(5), 1383–1388. <https://doi.org/10.3758/s13423-015-0814-7>
- Lewthwaite, R., & Wulf, G. (2010). Social-comparative feedback affects motor skill learning. *Quarterly Journal of Experimental Psychology*, 63(4), 738–749. <https://doi.org/10.1080/17470210903111839>
- Liebeskind, D. S. (2003). Collateral circulation. *Stroke*, 34(9), 2279–2284. <https://doi.org/10.1161/01.STR.0000086465.41263.06>
- Liepert, J. (2010). Evidence-based therapies for upper extremity dysfunction. *Current Opinion in Neurology*, 23(6), 678–682. <https://doi.org/10.1097/WCO.0b013e32833ff4c4>
- Liepert, J., Bauder, H., Miltner, W. H. R., Taub, E., & Weiller, C. (2000). Treatment-Induced cortical reorganization after stroke in humans. *Stroke*, 31(6), 1210–1216. <https://doi.org/10.1161/01.STR.31.6.1210>
- Liepert, J., Restemeyer, C., Kucinski, T., Zittel, S., & Weiller, C. (2005). Motor strokes: The lesion location determines motor excitability changes. *Stroke*, 36(12), 2648–2653. <https://doi.org/10.1161/01.STR.0000189629.10603.02>
- Liepert, Miltner, W. H., Bauder, H., Sommer, M., Dettmers, C., Taub, E., & Weiller, C. (1998a). Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neuroscience Letters*, 250(1), 5–8.
- Liepert, Miltner, W. H. R., Bauder, H., Sommer, M., Dettmers, C., Taub, E., & Weiller, C. (1998b). Motor cortex plasticity during constraint induced movement therapy in stroke patients. *Neuroscience Letters*, 250(1), 5–8. [https://doi.org/10.1016/S0304-3940\(98\)00386-3](https://doi.org/10.1016/S0304-3940(98)00386-3)
- Lin, K., Fu, T., Wu, C., Wang, Y., Liu, J., Hsieh, C., & Lin, S. (2010). Minimal Detectable Change and Clinically Important Difference of the Stroke Impact Scale in Stroke Patients. *Neurorehabilitation and Neural Repair*, 24(5), 486–492. <https://doi.org/10.1177/1545968309356295>
- Lisman, J. E., Grace, A. A., Nakajima, T., Taguchi, J., Ibata, Y., Duzel, E., ... Kandel, E. R. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*, 46(5), 703–713. <https://doi.org/10.1016/j.neuron.2005.05.002>
- Livingston-Thomas, J., Nelson, P., Karthikeyan, S., Antonescu, S., Jeffers, M. S., Marzolini, S., & Corbett, D. (2016). Exercise and Environmental Enrichment as Enablers of Task-Specific Neuroplasticity and Stroke Recovery. *Neurotherapeutics*, 13(2), 395–402. <https://doi.org/10.1007/s13311-016-0423-9>
- Logroscino, G., Capozzo, R., Tortelli, R., & Marin, B. (2016). Current Issues in Randomized Clinical Trials of Neurodegenerative Disorders at Enrolment and Reporting: Diagnosis, Recruitment, Representativeness of Patients, Ethnicity, and Quality of Reporting. *Frontiers of Neurology and Neuroscience*, 39, 24–36. <https://doi.org/10.1159/000445410>
- Lohse, K. R., Pathania, A., Wegman, R., Boyd, L. A., & Lang, C. E. (2018). On the Reporting of Experimental and Control Therapies in Stroke Rehabilitation Trials: A Systematic Review.

References

- Archives of Physical Medicine and Rehabilitation*.
<https://doi.org/10.1016/j.apmr.2017.12.024>
- Lotze, M., Scheler, G., Tan, H.-R. R. M., Braun, C., & Birbaumer, N. (2003). The musician's brain: Functional imaging of amateurs and professionals during performance and imagery. *NeuroImage*, 20(3), 1817–1829. <https://doi.org/10.1016/j.neuroimage.2003.07.018>
- Lovell, K., Bower, P., Richards, D., Barkham, M., Sibbald, B., Roberts, C., ... Hennessy, S. (2008). Developing guided self-help for depression using the Medical Research Council complex interventions framework: A description of the modelling phase and results of an exploratory randomised controlled trial. *BMC Psychiatry*, 8, 91. <https://doi.org/10.1186/1471-244X-8-91>
- Luker, J., Lynch, E., Bernhardsson, S., Bennett, L., & Bernhardt, J. (2015). Stroke Survivors' Experiences of Physical Rehabilitation: A Systematic Review of Qualitative Studies. *Archives of Physical Medicine and Rehabilitation*, 96(9), 1698–1708.e10. <https://doi.org/10.1016/j.apmr.2015.03.017>
- Lyle, R. C. (1981). A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *International Journal of Rehabilitation Research. Internationale Zeitschrift Für Rehabilitationsforschung. Revue Internationale de Recherches de Réadaptation*, 4(4), 483–492.
- Macleay, N., Pound, P., Wolfe, C., & Rudd, A. (2000). Qualitative analysis of stroke patients' motivation for rehabilitation. *BMJ*, 321(7268), 1051–1054.
- Magee, W. L., Clark, I., Tamplin, J., & Bradt, J. (2017). Music interventions for acquired brain injury. *Cochrane Database of Systematic Reviews*, 2017(1), CD006787. <https://doi.org/10.1002/14651858.CD006787.pub3>
- Magill, R. A., & Hall, K. G. (1990). A review of the contextual interference effect in motor skill acquisition. *Human Movement Science*, 9(3–5), 241–289. [https://doi.org/10.1016/0167-9457\(90\)90005-X](https://doi.org/10.1016/0167-9457(90)90005-X)
- Maldjian, J. A., Laurienti, P. J., & Burdette, J. H. (2004). Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *NeuroImage*, 21(1), 450–455. <https://doi.org/10.1016/j.neuroimage.2003.09.032>
- Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*, 19(3), 1233–1239. [https://doi.org/10.1016/S1053-8119\(03\)00169-1](https://doi.org/10.1016/S1053-8119(03)00169-1)
- Mandolesi, L., Gelfo, F., Serra, L., Montuori, S., Polverino, A., Curcio, G., & Sorrentino, G. (2017). Environmental factors promoting neural plasticity: Insights from animal and human studies. *Neural Plasticity*, 2017, 7219461. <https://doi.org/10.1155/2017/7219461>
- Marcheschi, E., Von Koch, L., Pessah-Rasmussen, H., & Elf, M. (2018). Home setting after stroke, facilitators and barriers: A systematic literature review. *Health Soc Care Community*, 26(4), e451-59. <https://doi.org/10.1111/hsc.12518>
- Marin, R. S., Biedrzycki, R. C., Firinciogullari, S., Rao, K., Price, T. R., & Stadlan, E. (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research*, 38(2), 143–162. [https://doi.org/10.1016/0165-1781\(91\)90040-V](https://doi.org/10.1016/0165-1781(91)90040-V)
- Mas-Herrero, E., Marco-Pallares, J., Lorenzo-Seva, U., Zatorre, R. J., & Rodriguez-Fornells, A. (2013). Individual Differences in Music Reward Experiences. *Music Perception: An Interdisciplinary Journal*, 31(2).
- Massy-Westropp, N. M., Gill, T. K., Taylor, A. W., Bohannon, R. W., & Hill, C. L. (2011). Hand Grip Strength: age and gender stratified normative data in a population-based study. *BMC Research Notes*, 4, 127. <https://doi.org/10.1186/1756-0500-4-127>

References

- Mathiowetz, V., Volland, G., Kashman, N., & Weber, K. (1985). Adult norms for the Box and Block Test of manual dexterity. *The American Journal of Occupational Therapy*, 39(6), 386–391.
- Mathiowetz, V., Weber, K., Volland, G., Kashman, N., & Cummings, R. (1984). Reliability and validity of grip and pinch strength evaluations. *The Journal of Hand Surgery*, 9(2), 222–226. [https://doi.org/10.1016/S0363-5023\(84\)80146-X](https://doi.org/10.1016/S0363-5023(84)80146-X)
- Mayo, N. E., Bronstein, D., Scott, S. C., Finch, L. E., & Miller, S. (2014). Necessary and sufficient causes of participation post-stroke: Practical and philosophical perspectives. *Quality of Life Research*, 23(1), 39–47. <https://doi.org/10.1007/s11136-013-0441-6>
- Mayo, N. E., Wood-Dauphinee, S., Carlton, R., Durcan, L., & Carlton, J. (2002). Activity, participation, and quality of life 6 months poststroke. *Archives of Physical Medicine and Rehabilitation*, 83(8), 1035–1042. <https://doi.org/10.1053/apmr.2002.33984>
- McCombe Waller, S., & Whittall, J. (2008). Bilateral arm training: why and who benefits? *NeuroRehabilitation*, 23(1), 29–41.
- McConnell, K. A., Nahas, Z., Shastri, A., Lorberbaum, J. P., Kozel, F. A., Bohning, D. E., & George, M. S. (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: A replication in healthy adults comparing two methods of assessing the distance to cortex. *Biological Psychiatry*, 49(5), 454–459. [https://doi.org/10.1016/S0006-3223\(00\)01039-8](https://doi.org/10.1016/S0006-3223(00)01039-8)
- McNair, D., Lorr, M., & Droppleman, L. (1971). *Manual for the profile of mood states*. San Diego, CA: Educational and Industrial Testing Services.
- Medical Research Council. (1976). *Aids to the Examination of the Peripheral Nervous System* (Vol. 38). London: The White Rose Press. <https://doi.org/10.1212/WNL.38.10.1663-a>
- Meister, I. G., Krings, T., Foltys, H., Boroojerdi, B., Müller, M., Töpper, R., & Thron, A. (2004). Playing piano in the mind - An fMRI study on music imagery and performance in pianists. *Cognitive Brain Research*, 19(3), 219–228. <https://doi.org/10.1016/j.cogbrainres.2003.12.005>
- Mellon, L., Hickey, A., Doyle, F., Dolan, E., & Williams, D. (2014). Can a media campaign change health service use in a population with stroke symptoms? Examination of the first Irish stroke awareness campaign. *Emergency Medicine Journal*, 31(7), 536–540. <https://doi.org/10.1136/emmermed-2012-202280>
- Mercier, C., Bertrand, A. M., & Bourbonnais, D. (2004). Differences in the magnitude and direction of forces during a submaximal matching in hemiparetic subjects. *Experimental Brain Research*, 157(1), 32–42. <https://doi.org/10.1007/s00221-003-1813-x>
- Meyer, S., Verheyden, G., Brinkmann, N., Dejaeger, E., De Weerd, W., Feys, H., ... De Wit, L. (2015). Functional and Motor Outcome 5 Years after Stroke Is Equivalent to Outcome at 2 Months: Follow-Up of the Collaborative Evaluation of Rehabilitation in Stroke Across Europe. *Stroke*, 46(6), 1613–1619. <https://doi.org/10.1161/STROKEAHA.115.009421>
- Michaelsen, S., Jacobs, S., Roby-Brami, A., & Levin, M. (2004). Compensation for distal impairments of grasping in adults with hemiparesis. *Experimental Brain Research*, 157(2), 162–173. <https://doi.org/10.1007/s00221-004-1829-x>
- Michielsen, M. E., Selles, R. W., Van Der Geest, J. N., Eckhardt, M., Yavuzer, G., Stam, H. J., ... Bussmann, J. B. J. (2011). Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: A phase II randomized controlled trial. *Neurorehabilitation and Neural Repair*, 25(3), 223–233. <https://doi.org/10.1177/1545968310385127>
- Moeller, T. B., & Reif, E. (2013). *Pocket Atlas of Sectional Anatomy: Computed Tomography and Magnetic Resonance Imaging. Volume I. Head and Neck* (Fourth Edi). New York: Thieme.
- Mohajerani, M. H., Aminoltejari, K., & Murphy, T. H. (2011). Targeted mini-strokes produce

References

- changes in interhemispheric sensory signal processing that are indicative of disinhibition within minutes. *Proceedings of the National Academy of Sciences*, 108(22), E183–E191. <https://doi.org/10.1073/pnas.1101914108>
- Möhler, R., Köpke, S., & Meyer, G. (2015). Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2). *Trials*, 16(1), 204. <https://doi.org/10.1186/s13063-015-0709-y>
- Muellbacher, W., Richards, C., Ziemann, U., Wittenberg, G., Wetz, D., Boroojerdi, B., ... Hallett, M. (2002). Improving hand function in chronic stroke. *Archives of Neurology*, 59(8), 1278–1282. <https://doi.org/10.1001/archneur.59.8.1278>
- Murase, N., Duque, J., Mazzocchio, R., & Cohen, L. G. (2004). Influence of Interhemispheric Interactions on Motor Function in Chronic Stroke. *Annals of Neurology*, 55(3), 400–409. <https://doi.org/10.1002/ana.10848>
- Murray, C. J. L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., ... Lopez, A. D. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, 380(9859), 2197–2223. [https://doi.org/10.1016/S0140-6736\(12\)61689-4](https://doi.org/10.1016/S0140-6736(12)61689-4)
- Mutai, H., Furukawa, T., Nakanishi, K., & Hanihara, T. (2016). Longitudinal functional changes, depression, and health-related quality of life among stroke survivors living at home after inpatient rehabilitation. *Psychogeriatrics*, 16(3), 185–190. <https://doi.org/10.1111/psyg.12137>
- Nadeau, S. E. (2002). A paradigm shift in neurorehabilitation. *The Lancet Neurology*, 1(2), 126–130.
- Nambu, I., Hagura, N., Hirose, S., Wada, Y., Kawato, M., & Naito, E. (2015). Decoding sequential finger movements from preparatory activity in higher-order motor regions: a functional magnetic resonance imaging multi-voxel pattern analysis. *European Journal of Neuroscience*, 42(10), 2851–2859. <https://doi.org/10.1111/ejn.13063>
- Netz, J., Lammers, T., & Hömberg, V. (1997). Reorganization of motor output in the non-affected hemisphere after stroke. *Brain*, 120(9), 1579–1586. <https://doi.org/10.1093/brain/120.9.1579>
- Nomura, E. M., Gratton, C., Visser, R. M., Kayser, A., Perez, F., & D'Esposito, M. (2010). Double dissociation of two cognitive control networks in patients with focal brain lesions. *Proceedings of the National Academy of Sciences*, 107(26), 12017–12022. <https://doi.org/10.1073/pnas.1002431107>
- Nudo, R. J. (2006). Plasticity. *NeuroRx*, 3(4), 420–427. <https://doi.org/10.1016/j.nurx.2006.07.006>
- Nudo, R. J., & Milliken, G. W. (1996). Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *Journal of Neurophysiology*, 75(5), 2144–2149. <https://doi.org/10.1152/jn.1996.75.5.2144>
- Nudo, R. J., Wise, B. M., SiFuentes, F., & Milliken, G. W. (1996). Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct. *Science*, 272(5269), 1791–1794. <https://doi.org/10.1126/science.272.5269.1791>
- Oakley, A., Strange, V., Bonell, C., Allen, E., & Stephenson, J. (2006). Process evaluation in randomised controlled trials of complex interventions. *British Medical Journal*, 332(7538), 413–416. <https://doi.org/10.1136/bmj.332.7538.413>
- Oliver, M. (1996). *Understanding disability: from theory to practice*. Basingstoke: Macmillan.
- Olsen, T. S. (1990). Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke*, 21(2), 247–251. <https://doi.org/10.1161/01.STR.21.2.247>

References

- Outpatient Service Trialists. (2003). Therapy-based rehabilitation services for stroke patients at home. *Cochrane Database of Systematic Reviews*, (1), CD002925. <https://doi.org/10.1002/14651858.CD002925>
- Paciaroni, M., Agnelli, G., Corea, F., Ageno, W., Alberti, A., Lanari, A., ... Silvestrelli, G. (2008). Early hemorrhagic transformation of brain infarction: Rate, predictive factors, and influence on clinical outcome: Results of a prospective multicenter study. *Stroke*, 39(8), 2249–2256. <https://doi.org/10.1161/STROKEAHA.107.510321>
- Page, S. J., Murray, C., Hermann, V., & Levine, P. (2011). Retention of motor changes in chronic stroke survivors who were administered mental practice. *Archives of Physical Medicine and Rehabilitation*, 92(11), 1741–1745. <https://doi.org/10.1016/j.apmr.2011.06.009>
- Pantev, C., & Herholz, S. C. (2011). Plasticity of the human auditory cortex related to musical training. *Neuroscience & Biobehavioral Reviews*, 35(10), 2140–2154. <https://doi.org/10.1016/j.neubiorev.2011.06.010>
- Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology*, 9(7), 689–701. [https://doi.org/10.1016/S1474-4422\(10\)70104-6](https://doi.org/10.1016/S1474-4422(10)70104-6)
- Panzer, S., Krueger, M., Muehlbauer, T., Kovacs, A. J., & Shea, C. H. (2009). Inter-manual transfer and practice: Coding of simple motor sequences. *Acta Psychologica*, 131(2), 99–109. <https://doi.org/10.1016/j.actpsy.2009.03.004>
- Parker, V. M., Wade, D. T., & Langton Hewer, R. (1986). Loss of arm function after stroke: measurement, frequency, and recovery. *International Rehabilitation Medicine*, 8(2), 69–73.
- Pascual-Leone, A., Grafman, J., & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science*, 263(5151), 1287–1289. <https://doi.org/10.1126/science.8122113>
- Pascual-Leone, Dang, N., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., Hallett, M., ... Hallett, M. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *Journal of Neurophysiology*, 74(3), 1037–1045. <https://doi.org/10.1152/jn.1995.74.3.1037>
- Patel, A. D. (2006). Musical Rhythm, Linguistic Rhythm, and Human Evolution. *Music Perception*, 24(1), 99–104. <https://doi.org/10.1525/mp.2006.24.1.99>
- Patel, A. D. (2011). Why would musical training benefit the neural encoding of speech? The OPERA hypothesis. *Frontiers in Psychology*. <https://doi.org/10.3389/fpsyg.2011.00142>
- Patrick, D. L., & Erickson, P. (1993). *Health status and health policy*. New York: Oxford University Press.
- Pauwels, L., Swinnen, S. P., & Beets, I. A. M. (2014). Contextual interference in complex bimanual skill learning leads to better skill persistence. *PLoS ONE*, 9(6), e100906. <https://doi.org/10.1371/journal.pone.0100906>
- Pearce, A. J., Thickbroom, G. W., Byrnes, M. L., & Mastaglia, F. L. (2000). Functional reorganisation of the corticomotor projection to the hand in skilled racquet players. *Experimental Brain Research*, 130(2), 238–243. <https://doi.org/10.1007/s002219900236>
- Pekna, M., Pekny, M., & Nilsson, M. (2012). Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke*, 43(10), 2819–2828. <https://doi.org/10.1161/STROKEAHA.112.654228>
- Penhune, V. B., & Steele, C. J. (2011). Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning. *Behavioural Brain Research*, 226(2010), 579–591. <https://doi.org/10.1016/j.bbr.2011.09.044>

References

- Pereira, S., Ross Graham, J., Shahabaz, A., Salter, K., Foley, N., Meyer, M., & Teasell, R. (2012). Rehabilitation of Individuals With Severe Stroke: Synthesis of Best Evidence and Challenges in Implementation. *Topics in Stroke Rehabilitation, 19*(2), 122–131. <https://doi.org/10.1310/tsr1902-122>
- Perenboom, R. J. M., & Chorus, A. M. J. (2003). Measuring participation according to the International Classification of Functioning, Disability and Health (ICF). *Disability and Rehabilitation, 25*(11–12), 577–587. <https://doi.org/10.1080/0963828031000137081>
- Perez, M. A., Tanaka, S., Wise, S. P., Sadato, N., Tanabe, H. C., Willingham, D. T., & Cohen, L. G. (2007). Neural Substrates of Intermanual Transfer of a Newly Acquired Motor Skill. *Current Biology, 17*(21), 1896–1902. <https://doi.org/10.1016/j.cub.2007.09.058>
- Perez, M. A., Tanaka, S., Wise, S. P., Willingham, D. T., & Cohen, L. G. (2008). Time-Specific Contribution of the Supplementary Motor Area to Intermanual Transfer of Procedural Knowledge. *Journal of Neuroscience, 28*(39), 9664–9669. <https://doi.org/10.1523/JNEUROSCI.3416-08.2008>
- Perlmutter, D., & Rhoton, A. L. (1976). Microsurgical anatomy of the anterior cerebral-anterior communicating-recurrent artery complex. *Journal of Neurosurgery, 45*(3), 259–272. <https://doi.org/10.3171/jns.1976.45.3.0259>
- Pineiro, R., Pendlebury, S., Johansen-Berg, H., & Matthews, P. M. (2001). Functional MRI detects posterior shifts in primary sensorimotor cortex activation after stroke: Evidence of local adaptive reorganization? *Stroke, 32*(5), 1134–1139. <https://doi.org/10.1161/01.STR.32.5.1134>
- Plant, S. E., Tyson, S. F., Kirk, S., & Parsons, J. (2016). What are the barriers and facilitators to goal-setting during rehabilitation for stroke and other acquired brain injuries? A systematic review and meta-synthesis. *Clinical Rehabilitation, 30*(9), 921–930. <https://doi.org/10.1177/0269215516655856>
- Plautz, E. J., Milliken, G. W., & Nudo, R. J. (2000). Effects of repetitive motor training on movement representations in adult squirrel monkeys: Role of use versus learning. *Neurobiology of Learning and Memory, 74*(1), 27–55. <https://doi.org/10.1006/nlme.1999.3934>
- Ploughman, M., Granter-Button, S., Chernenko, G., Tucker, B. A., Mearow, K. M., & Corbett, D. (2005). Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-I and insulin-like growth factor I after focal ischemia. *Neuroscience, 136*(4), 991–1001. <https://doi.org/10.1016/j.neuroscience.2005.08.037>
- Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., & van Wijck, F. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews, 11*(11), CD010820-CD010820. <https://doi.org/10.1002/14651858.CD010820.pub2.www.cochranelibrary.com>
- Poltawski, L., Boddy, K., Forster, A., Goodwin, V. A., Pavey, A. C., & Dean, S. (2015). Motivators for uptake and maintenance of exercise: Perceptions of long-term stroke survivors and implications for design of exercise programmes. *Disability and Rehabilitation, 37*(9), 795–801. <https://doi.org/10.3109/09638288.2014.946154>
- Pomeroy, V., Aglioti, S. M., Mark, V. W., McFarland, D., Stinear, C., Wolf, S. L., ... Fitzpatrick, S. M. (2011). Neurological principles and rehabilitation of action disorders: rehabilitation interventions. *Neurorehabilitation and Neural Repair, 25*(5 Suppl), 33S–43S. <https://doi.org/10.1177/1545968311410942>
- Puig, J., Blasco, G., Schlaug, G., Stinear, C. M., Daunis-i-Estadella, P., Biarnes, C., ... Pedraza, S. (2017). Diffusion tensor imaging as a prognostic biomarker for motor recovery and rehabilitation after stroke. *Neuroradiology, 59*(4), 343–351.

References

- <https://doi.org/10.1007/s00234-017-1816-0>
- Raghavan, P., Geller, D., Guerrero, N., Aluru, V., Eimicke, J. P., Teresi, J. A., ... Turry, A. (2016). Music Upper Limb Therapy—Integrated: An Enriched Collaborative Approach for Stroke Rehabilitation. *Frontiers in Human Neuroscience*, *10*, 498. <https://doi.org/10.3389/fnhum.2016.00498>
- Raglio, A., Zaliani, A., Baiardi, P., Bossi, D., Sguazzin, C., Capodaglio, E., ... Imbriani, M. (2017). Active music therapy approach for stroke patients in the post-acute rehabilitation. *Neurological Sciences*, *38*(5), 893–897. <https://doi.org/10.1007/s10072-017-2827-7>
- Rand, M. K., Hikosaka, O., Miyachi, S., Lu, X., & Miyashita, K. (1998). Characteristics of a long-term procedural skill in the monkey. *Experimental Brain Research*, *118*(3), 293–297. <https://doi.org/10.1007/s002210050284>
- Rathore, S. S., Hinn, A. R., Cooper, L. S., Tyroler, H. A., & Rosamond, W. D. (2002). Characterization of incident stroke signs and symptoms findings from the atherosclerosis risk in communities study. *Stroke*, *33*(11), 2718–2721. <https://doi.org/10.1161/01.STR.0000035286.87503.31>
- Rehme, A. K., Eickhoff, S. B., Rottschy, C., Fink, G. R., & Grefkes, C. (2012). Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. *NeuroImage*, *59*(3), 2771–2782. <https://doi.org/10.1016/j.neuroimage.2011.10.023>
- Reinkensmeyer, D. J., Burdet, E., Casadio, M., Krakauer, J. W., Kwakkel, G., Lang, C. E., ... Schweighofer, N. (2016). Computational neurorehabilitation: modeling plasticity and learning to predict recovery. *Journal of Neuroengineering and Rehabilitation*, *13*(1), 42. <https://doi.org/10.1186/s12984-016-0148-3>
- Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor Skills*, *8*(3), 271–276. <https://doi.org/10.2466/pms.1958.8.3.271>
- Rey, A. (1964). *L'examen Clinique en Psychologie* (2e éd.). Paris: Presses universitaires de France.
- Richards, M., & Sacker, A. (2010). Neuropsychology Lifetime Antecedents of Cognitive Reserve. *Journal of Clinical and Experimental Neuropsychology*, *25*, 37–41. <https://doi.org/10.1076/jcen.25.5.614.14581>
- Riecker, A., Gröschel, K., Ackermann, H., Schnaudigel, S., Kassubek, J., & Kastrup, A. (2010). The role of the unaffected hemisphere in motor recovery after stroke. *Human Brain Mapping*, *31*(7), 1017–1029. <https://doi.org/10.1002/hbm.20914>
- Ringelstein, E. B., Chamorro, A., Kaste, M., Langhorne, P., Leys, D., Lyrer, P., ... Toni, D. (2013). European stroke organisation recommendations to establish a stroke unit and stroke center. *Stroke*, *44*(3), 828–840. <https://doi.org/10.1161/STROKEAHA.112.670430>
- Ripollés, P., Marco-Pallarés, J., Alicart, H., Tempelmann, C., Rodríguez-Fornells, A., & Noesselt, T. (2016). Intrinsic monitoring of learning success facilitates memory encoding via the activation of the SN/VTA-Hippocampal loop. *ELife*, *5*. <https://doi.org/10.7554/eLife.17441>
- Ripollés, P., Marco-Pallarés, J., Hielscher, U., Mestres-Missé, A., Tempelmann, C., Heinze, H. J., ... Noesselt, T. (2014). The role of reward in word learning and its implications for language acquisition. *Current Biology*, *24*(21), 2606–2611. <https://doi.org/10.1016/j.cub.2014.09.044>
- Ripollés, P., Rojo, N., Grau-Sánchez, J., Amengual, J. L. L., Càmara, E., Marco-Pallarés, J., ... Rodríguez-Fornells, A. (2016). Music supported therapy promotes motor plasticity in individuals with chronic stroke. *Brain Imaging and Behavior*, *10*(4), 1289–1307. <https://doi.org/10.1007/s11682-015-9498-x>
- Robertson, E. M., Pascual-Leone, A., & Miall, R. C. (2004). Current concepts in procedural consolidation. *Nature Reviews Neuroscience*, *5*(7), 576–582.

References

- <https://doi.org/10.1038/nrn1426>
- Rodgers, H. (2013). Stroke. In M. P. Barnes & D. C. Good (Eds.), *Handbook of Clinical Neurology* (pp. 427–433). Elsevier B.V. <https://doi.org/10.1016/B978-0-444-52901-5.00036-8>
- Rodgers, H., & Price, C. (2017). Stroke unit care, inpatient rehabilitation and early supported discharge. *Clinical Medicine*, 17(2), 173–177. <https://doi.org/10.7861/clinmedicine.17-2-173>
- Rodriguez-Fornells, A., Rojo, N., Amengual, J. L., Ripollés, P., Altenmüller, E., & Münte, T. F. (2012). The involvement of audio-motor coupling in the music-supported therapy applied to stroke patients. *Annals of the New York Academy of Sciences*, 1252(1), 282–293. <https://doi.org/10.1111/j.1749-6632.2011.06425.x>
- Rojkova, K., Volle, E., Urbanski, M., Humbert, F., Dell’Acqua, F., & Thiebaut de Schotten, M. (2016). Atlasing the frontal lobe connections and their variability due to age and education: a spherical deconvolution tractography study. *Brain Structure and Function*, 221(3), 1751–1766. <https://doi.org/10.1007/s00429-015-1001-3>
- Rojo, N., Amengual, J., Juncadella, M., Rubio, F., Camara, E., Marco-Pallares, J., ... Rodriguez-Fornells, A. (2011). Music-supported therapy induces plasticity in the sensorimotor cortex in chronic stroke: a single-case study using multimodal imaging (fMRI-TMS). *Brain Injury*, 25(7–8), 787–793. <https://doi.org/10.3109/02699052.2011.576305>
- Rosenzweig, S., & Carmichael, S. T. (2015). The axon-glia unit in white matter stroke: mechanisms of damage and recovery. *Brain Research*, 1623, 123–134. <https://doi.org/10.1016/j.brainres.2015.02.019>
- Ross, R. (1993). The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*, 362(6423), 801–809. <https://doi.org/10.1038/362801a0>
- Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, 120(12), 2008–2039. <https://doi.org/10.1016/j.clinph.2009.08.016>
- Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., ... Tomberg, C. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, 91(2), 79–92. [https://doi.org/10.1016/0013-4694\(94\)90029-9](https://doi.org/10.1016/0013-4694(94)90029-9)
- Saemi, E., Porter, J. M., Ghotbi-Varzaneh, A., Zarghami, M., & Maleki, F. (2012). Knowledge of results after relatively good trials enhances self-efficacy and motor learning. *Psychology of Sport and Exercise*, 13(4), 378–382. <https://doi.org/10.1016/j.psychsport.2011.12.008>
- Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., & Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nature Neuroscience*, 14(2), 257–264. <https://doi.org/10.1038/nn.2726>
- Salimpoor, V. N., Benovoy, M., Longo, G., Cooperstock, J. R., & Zatorre, R. J. (2009). The rewarding aspects of music listening are related to degree of emotional arousal. *PLoS ONE*, 4(10), e7487–e7487. <https://doi.org/10.1371/journal.pone.0007487>
- Salimpoor, V. N., van den Bosch, I., Kovacevic, N., McIntosh, A. R., Dagher, A., & Zatorre, R. J. (2013). Interactions Between the Nucleus Accumbens and Auditory Cortices Predict Music Reward Value. *Science*, 340(6129), 216–219. <https://doi.org/10.1126/science.1231059>
- Salimpoor, V. N., Zald, D. H., Zatorre, R. J., Dagher, A., & McIntosh, A. R. (2015). Predictions and the brain: how musical sounds become rewarding. *Trends in Cognitive Sciences*, 19(2), 86–91. <https://doi.org/10.1016/j.tics.2014.12.001>

References

- Salter, K. L., Foley, N. C., Jutai, J. W., & Teasell, R. W. (2007). Assessment of participation outcomes in randomized controlled trials of stroke rehabilitation interventions. *International Journal of Rehabilitation Research*, 30(4), 339–342. <https://doi.org/10.1097/MRR.0b013e3282f144b7>
- Sanes, J. N., & Donoghue, J. P. (2000). Plasticity and Primary Motor Cortex. *Annual Review of Neuroscience*, 23(1), 393–415. <https://doi.org/10.1146/annurev.neuro.23.1.393>
- Sanson-Fisher, R. W., Bonevski, B., Green, L. W., & D'Este, C. (2007). Limitations of the Randomized Controlled Trial in Evaluating Population-Based Health Interventions. *American Journal of Preventive Medicine*, 33(2), 155–161. <https://doi.org/10.1016/j.amepre.2007.04.007>
- Saposnik, G., Cohen, L. G., Mamdani, M., Pooyania, S., Ploughman, M., Cheung, D., ... Stroke Outcomes Research Canada. (2016). Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. *The Lancet Neurology*, 15(10), 1019–1027. [https://doi.org/10.1016/S1474-4422\(16\)30121-1](https://doi.org/10.1016/S1474-4422(16)30121-1)
- Särkämö, T. (2016). Cognitive, emotional, and neural benefits of musical leisure activities in aging and neurological rehabilitation: A critical review. *Annals of Physical and Rehabilitation Medicine*. <https://doi.org/10.1016/j.rehab.2017.03.006>
- Särkämö, T., Pihko, E., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., ... Tervaniemi, M. (2010). Music and speech listening enhance the recovery of early sensory processing after stroke. *Journal of Cognitive Neuroscience*, 22(12), 2716–2727. <https://doi.org/10.1162/jocn.2009.21376>
- Särkämö, T., Ripollés, P., Vepsäläinen, H., Autti, T., Silvennoinen, H. M., Salli, E., ... Rodríguez-Fornells, A. (2014). Structural changes induced by daily music listening in the recovering brain after middle cerebral artery stroke: a voxel-based morphometry study. *Frontiers in Human Neuroscience*, 8, 245. <https://doi.org/10.3389/fnhum.2014.00245>
- Särkämö, T., & Soto, D. (2012). Music listening after stroke: Beneficial effects and potential neural mechanisms. *Annals of the New York Academy of Sciences*, 1252(1), 266–281. <https://doi.org/10.1111/j.1749-6632.2011.06405.x>
- Särkämö, T., Tervaniemi, M., Huotilainen, M., Särkämö, T., Tervaniemi, M., & Huotilainen, M. (2013). Music perception and cognition: Development, neural basis, and rehabilitative use of music. *Wiley Interdisciplinary Reviews: Cognitive Science*, 4(4), 441–451. <https://doi.org/10.1002/wcs.1237>
- Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., ... Hietanen, M. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain*, 131(3), 866–876. <https://doi.org/10.1093/brain/awn013>
- Särkämö, T., Tervaniemi, M., Laitinen, S., Numminen, A., Kurki, M., Johnson, J. K., & Rantanen, P. (2014). Cognitive, emotional, and social benefits of regular musical activities in early dementia: Randomized controlled study. *Gerontologist*, 54(4), 634–650. <https://doi.org/10.1093/geront/gnt100>
- Sarre, S., Redlich, C., Tinker, A., Sadler, E., Bhalla, A., & McKeivitt, C. (2014). A systematic review of qualitative studies on adjusting after stroke: lessons for the study of resilience. *Disability and Rehabilitation*, 36(9), 716–726. <https://doi.org/10.3109/09638288.2013.814724>
- Savion-Lemieux, T., & Penhune, V. B. (2005). The effects of practice and delay on motor skill learning and retention. *Experimental Brain Research*, 161(4), 423–431. <https://doi.org/10.1007/s00221-004-2085-9>
- Schiene, K., Bruehl, C., Zilles, K., Qu, M., Hagemann, G., Kraemer, M., & Witte, O. W. (1996). Neuronal Hyperexcitability and Reduction of GABA A -Receptor Expression in the Surround

References

- of Cerebral Photothrombosis. *Journal of Cerebral Blood Flow & Metabolism*, 16(5), 906–914. <https://doi.org/10.1097/00004647-199609000-00014>
- Schlaug, G. (2015). Musicians and music making as a model for the study of brain plasticity. *Progress in Brain Research*, 217, 37–55. <https://doi.org/10.1016/bs.pbr.2014.11.020>
- Schneider, S., Schönle, P. ., Altenmüller, E., & Münte, T. . (2007). Using musical instruments to improve motor skill recovery following a stroke. *Journal of Neurology*, 254(10), 1339–1346. <https://doi.org/10.1007/s00415-006-0523-2>
- Scholz, D. S., Rohde, S., Nikmaram, N., Brückner, H.-P. P., Großbach, M., Rollnik, J. D., & Altenmüller, E. (2016). Sonification of arm movements in stroke rehabilitation - a novel approach in neurologic music therapy. *Frontiers in Neurology*, 7, 106. <https://doi.org/10.3389/fneur.2016.00106>
- Selzer, M. E., Clarke, S., Cohen, L. G., Duncan, P. W., & Cage, F. G. (2006). *Textbook of Neural Repair and Rehabilitation* (Vol. 2). Cambridge: Cambridge University Press. <https://doi.org/10.1017/CBO9780511545078>
- Shadmehr, R., & Brashers-Krug, T. (1997). Functional stages in the formation of human long-term motor memory. *The Journal of Neuroscience*, 17(1), 409–419. <https://doi.org/10.1523/JNEUROSCI.17-01-00409.1997>
- Sharma, V. K., & Wong, L. K. S. (2016). Middle Cerebral Artery Disease. In J. C. Grotta, G. W. Albers, J. P. Broderick, S. E. Kasner, A. Eng H Lo, D. Mendelow, ... L. K. Wong (Eds.), *Stroke: Pathophysiology, Diagnosis, and Management* (Sixth Edit). Elsevier Inc. <https://doi.org/10.1016/B978-0-323-29544-4.00024-4>
- Shea, C. H., Kovacs, A. J., & Panzer, S. (2011). The Coding and Inter-Manual Transfer of Movement Sequences. *Frontiers in Psychology*, 2, 52. <https://doi.org/10.3389/fpsyg.2011.00052>
- Shea, J. B., & Morgan, R. L. (1979). Contextual interference effects on the acquisition, retention, and transfer of a motor skill. *Journal of Experimental Psychology: Human Learning & Memory*, 5(2), 179–187. <https://doi.org/10.1037/0278-7393.5.2.179>
- Sihvonen, A. J., Särkämö, T., Leo, V., Tervaniemi, M., Altenmüller, E., & Soinila, S. (2017). Music-based interventions in neurological rehabilitation. *The Lancet Neurology*, 16(8), 648–660. [https://doi.org/10.1016/S1474-4422\(17\)30168-0](https://doi.org/10.1016/S1474-4422(17)30168-0)
- Smith, J. D. (2012). Single-case experimental designs: a systematic review of published research and current standards. *Psychological Methods*, 17(4), 510–550. <https://doi.org/10.1037/a0029312>
- Sommer, C. J., & Schäbitz, W. R. (2017). Fostering Poststroke Recovery: Towards Combination Treatments. *Stroke*, 48(4), 1112–1119. <https://doi.org/10.1161/STROKEAHA.116.013324>
- Sozmen, E. G., Hinman, J. D., & Carmichael, S. T. (2012, April). Models That Matter: White Matter Stroke Models. *Neurotherapeutics*. Springer. <https://doi.org/10.1007/s13311-012-0106-0>
- Staff, R. T., Murray, A. D., Deary, I. J., & Whalley, L. J. (2004). What provides cerebral reserve? *Brain*, 127(5), 1191–1199. <https://doi.org/10.1093/brain/awh144>
- Steele, C. J., Bailey, J. a., Zatorre, R. J., & Penhune, V. B. (2013). Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. *Journal of Neuroscience*, 33(3), 1282–1290. <https://doi.org/10.1523/JNEUROSCI.3578-12.2013>
- Steffener, J., & Stern, Y. (2012). Exploring the neural basis of cognitive reserve in aging. *Biochimica et Biophysica Acta*, 1822(3), 467–473. <https://doi.org/10.1016/j.bbadis.2011.09.012>
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, 8(3), 448–460.

References

- <https://doi.org/10.1017/S1355617702813248>
- Stevens, E., Emmett, E., Yanzhong, W., McKeivitt, C. J., & Wolfe, C. D. A. (2017). *The burden of stroke in Europe*. King's College London, Stroke Alliance For Europe. Retrieved from <http://www.strokeeurope.eu/downloads/TheBurdenOfStrokeInEuropeReport.pdf>
- Stewart, K. C., Cauraugh, J. H., & Summers, J. J. (2006). Bilateral movement training and stroke rehabilitation: a systematic review and meta-analysis. *Journal of the Neurological Sciences*, 244(1–2), 89–95. <https://doi.org/10.1016/j.jns.2006.01.005>
- Stinear, C. (2010). Prediction of recovery of motor function after stroke. *Lancet Neurology*, 9(12), 1228–1232. [https://doi.org/10.1016/S1474-4422\(10\)70247-7](https://doi.org/10.1016/S1474-4422(10)70247-7)
- Stokes, T. F., & Baer, D. M. (1977). An implicit technology of generalization. *Journal of Applied Behavior Analysis*, 10(2), 349–367. <https://doi.org/10.1901/JABA.1977.10-349>
- Street, A. J., Magee, W. L., Bateman, A., Parker, M., Odell-Miller, H., & Fachner, J. (2018). Home-based neurologic music therapy for arm hemiparesis following stroke: results from a pilot, feasibility randomized controlled trial. *Clinical Rehabilitation*, 32(1), 18–28. <https://doi.org/10.1177/0269215517717060>
- Street, A. J., Magee, W. L., Odell-Miller, H., Bateman, A., & Fachner, J. C. (2015). Home-based neurologic music therapy for upper limb rehabilitation with stroke patients at community rehabilitation stage—a feasibility study protocol. *Frontiers in Human Neuroscience*, 9, 480. <https://doi.org/10.3389/fnhum.2015.00480>
- Stroemer, R. P., Kent, T. A., & Hulsebosch, C. E. (1995). Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. *Stroke*, 26(11), 2135–2144. <https://doi.org/10.1161/01.STR.26.11.2135>
- Stroke Unit Trialists' Collaboration. (2013). Organised inpatient (stroke unit) care for stroke. *The Cochrane Database of Systematic Reviews*, 9, CD000197. <https://doi.org/10.1002/14651858.CD000197.pub3>
- Stroop, J. R. (1992). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 121(1), 15–23.
- Sugawara, S. K., Tanaka, S., Okazaki, S., Watanabe, K., & Sadato, N. (2012). Social Rewards Enhance Offline Improvements in Motor Skill. *PLoS ONE*, 7(11), e48174. <https://doi.org/10.1371/journal.pone.0048174>
- Sun, H., Blakely, T. M., Darvas, F., Wander, J. D., Johnson, L. A., Su, D. K., ... Ojemann, J. G. (2015). Sequential activation of premotor, primary somatosensory and primary motor areas in humans during cued finger movements. *Clinical Neurophysiology*, 126(11), 2150–2161. <https://doi.org/10.1016/j.clinph.2015.01.005>
- Talelli, P., Greenwood, R. J., & Rothwell, J. C. (2006). Arm function after stroke: Neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clinical Neurophysiology*, 117(8), 1641–1659. <https://doi.org/10.1016/j.clinph.2006.01.016>
- Taub, E., Miller, N. E., Novack, T. A., Cook, E. W., Fleming, W. C., Nepomuceno, C. S., ... Crago, J. E. (1993). Technique to improve chronic motor deficit after stroke. *Archives of Physical Medicine and Rehabilitation*, 74(4), 347–354. <https://doi.org/8466415>
- Taub, E., & Morris, D. M. (2001). Constraint-induced movement therapy to enhance recovery after stroke. *Current Atherosclerosis Reports*, 3(4), 279–286. <https://doi.org/10.1007/s11883-001-0020-0>
- Taub, E., Uswatte, G., & Elbert, T. (2002). New treatments in neurorehabilitation founded on basic research. *Nature Reviews Neuroscience*, 3(3), 228–236. <https://doi.org/10.1038/nrn754>

References

- Taub, E., Uswatte, G., & Pidikiti, R. (1999). Constraint-Induced Movement Therapy: A New Family of Techniques with Broad Application to Physical Rehabilitation-A Clinical Review. *Journal of Rehabilitation Research and Development*, 36(3), 237–251.
- Teasell, R., Bayona, N. A., & Bitensky, J. (2005). Plasticity and Reorganization of the Brain Post Stroke. *Topics in Stroke Rehabilitation*, 12(3), 11–26. <https://doi.org/10.1310/6AUM-ETYW-Q8XV-8XAC>
- Thabit, M. N., Nakatsuka, M., Koganemaru, S., Fawi, G., Fukuyama, H., & Mima, T. (2011). Momentary reward induce changes in excitability of primary motor cortex. *Clinical Neurophysiology*, 122(9), 1764–1770. <https://doi.org/10.1016/j.clinph.2011.02.021>
- Thiebaut De Schotten, M., Tomaiuolo, F., Aiello, M., Merola, S., Silvetti, M., Lecce, F., ... Doricchi, F. (2014). Damage to white matter pathways in subacute and chronic spatial neglect: A group study and 2 single-case studies with complete virtual “in vivo” tractography dissection. *Cerebral Cortex*, 24(3), 691–706. <https://doi.org/10.1093/cercor/bhs351>
- Thielman, G. T., Dean, C. M., & Gentile, A. M. (2004). Rehabilitation of reaching after stroke: Task-related training versus progressive resistive exercise. *Archives of Physical Medicine and Rehabilitation*, 85(10), 1613–1618. <https://doi.org/10.1016/j.apmr.2004.01.028>
- Thomalla, G., Glauche, V., Koch, M. A., Beaulieu, C., Weiller, C., & Röther, J. (2004). Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. *NeuroImage*, 22(4), 1767–1774. <https://doi.org/10.1016/j.neuroimage.2004.03.041>
- Timmermans, A. A. A., Spooren, A. I. F., Kingma, H., & Seelen, H. A. M. Influence of task-oriented training content on skilled arm-hand performance in stroke: a systematic review. *Neurorehabilitation and Neural Repair*, 24(9), 858–870. <https://doi.org/10.1177/1545968310368963>
- Tong, Y., Forreider, B., Sun, X., Geng, X., Zhang, W., Du, H., ... Ding, Y. (2015). Music-supported therapy (MST) in improving post-stroke patients’ upper-limb motor function: a randomised controlled pilot study. *Neurological Research*, 37(5), 434–440. <https://doi.org/10.1179/1743132815Y.0000000034>
- Traversa, R., Cicinelli, P., Bassi, A., Rossini, P. M., & Bernardi, G. (1997). Mapping of Motor Cortical Reorganization After Stroke: A Brain Stimulation Study With Focal Magnetic Pulses. *Stroke*, 28(1), 110–117. <https://doi.org/10.1161/01.STR.28.1.110>
- Traversa, R., Cicinelli, P., Pasqualetti, P., Filippi, M., & Rossini, P. M. (1998). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain Research*, 803(1–2), 1–8. [https://doi.org/10.1016/S0006-8993\(98\)00505-8](https://doi.org/10.1016/S0006-8993(98)00505-8)
- Traversa, R., Cicinelli, P., Pasqualetti, P., Filippi, M., & Rossini, P. M. (1998). Follow-up of interhemispheric differences of motor evoked potentials from the “affected” and “unaffected” hemispheres in human stroke. *Brain Research*, 803(1–2), 1–8. [https://doi.org/10.1016/S0006-8993\(98\)00505-8](https://doi.org/10.1016/S0006-8993(98)00505-8)
- Truelsen, T., Ekman, M., & Boysen, G. (2005). Cost of stroke in Europe. *European Journal of Neurology*, 12(Suppl. 1), 78–84. <https://doi.org/10.1111/j.1468-1331.2005.01199.x>
- Truelsen, T., Piechowski-Jóźwiak, B., Bonita, R., Mathers, C., Bogousslavsky, J., & Boysen, G. (2006). Stroke incidence and prevalence in Europe: A review of available data. *European Journal of Neurology*, 13(6), 581–598. <https://doi.org/10.1111/j.1468-1331.2006.01138.x>
- Turton, A., & Pomeroy, V. (2002). When should upper limb function be trained after stroke? Evidence for and against early intervention. *NeuroRehabilitation*, 17(3), 215–224.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage*, 15(1), 273–289.

References

- <https://doi.org/10.1006/nimg.2001.0978>
- United Nations. (2006). *Convention on the rights of persons with disabilities. Treaty Series* (Vol. 2515). Retrieved from <http://www.un.org/disabilities/documents/convention/convoptprot-e.pdf>
- Vafadar, A. K., Côté, J. N., & Archambault, P. S. (2015). Effectiveness of functional electrical stimulation in improving clinical outcomes in the upper arm following stroke: A systematic review and meta-analysis. *BioMed Research International*, 2015, 1–14. <https://doi.org/10.1155/2015/729768>
- van der Lee, J. H., Beckerman, H., Lankhorst, G. J., & Bouter, L. M. (2001). The responsiveness of the Action Research Arm test and the Fugl-Meyer Assessment scale in chronic stroke patients. *Journal of Rehabilitation Medicine*, 33(3), 110–113.
- Van Kordelaar, J., Van Wegen, E., & Kwakkel, G. (2014). Impact of time on quality of motor control of the paretic upper limb after stroke. *Archives of Physical Medicine and Rehabilitation*, 95(2), 338–344. <https://doi.org/10.1016/j.apmr.2013.10.006>
- Van Peppen, R. P. S., Kwakkel, G., Wood-Dauphinee, S., Hendriks, H. J. M., Van der Wees, P. J., & Dekker, J. (2004). The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clinical Rehabilitation*, 18(8), 833–862. <https://doi.org/10.1191/0269215504cr843oa>
- Van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H., & Van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, 19(5), 604–607. <https://doi.org/10.1161/01.STR.19.5.604>
- Van Vugt, F. T., Kafczyk, T., Kuhn, W., Rollnik, J. D., Tillmann, B., & Altenmüller, E. (2016). The role of auditory feedback in music-supported stroke rehabilitation: A single-blinded randomised controlled intervention. *Restorative Neurology and Neuroscience*, 34(2), 297–311. <https://doi.org/10.3233/RNN-150588>
- Van Vugt, F. T., Ritter, J., Rollnik, J. D., & Altenmüller, E. (2014). Music-supported motor training after stroke reveals no superiority of synchronization in group therapy. *Frontiers in Human Neuroscience*, 8, 315. <https://doi.org/10.3389/fnhum.2014.00315>
- Vargus-Adams, J. N., & Majnemer, A. (2014). International Classification of Functioning, Disability and Health (ICF) as a Framework for Change: Revolutionizing Rehabilitation Overview of the Classification. *Journal of Child Neurology*, 29(8), 1030–1035. <https://doi.org/10.1177/0883073814533595>
- Veerbeek, J. M., Langbroek-Amersfoort, A. C., van Wegen, E. E. H., Meskers, C. G. M., & Kwakkel, G. (2017). Effects of Robot-Assisted Therapy for the Upper Limb After Stroke. *Neurorehabilitation and Neural Repair*, 31(2), 107–121. <https://doi.org/10.1177/1545968316666957>
- Vergheze, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., ... Buschke, H. (2003). Leisure Activities and the Risk of Dementia in the Elderly. *New England Journal of Medicine*, 348(25), 2508–2516. <https://doi.org/10.1056/NEJMoa022252>
- Villeneuve, M., & Lamontagne, A. (2013). Playing piano can improve upper extremity function after stroke: Case studies. *Stroke Research and Treatment*, 2013, 159105. <https://doi.org/10.1155/2013/159105>
- Villeneuve, M., Penhune, V., & Lamontagne, A. (2014). A Piano Training Program to Improve Manual Dexterity and Upper Extremity Function in Chronic Stroke Survivors. *Frontiers in Human Neuroscience*, 8, 662. <https://doi.org/10.3389/fnhum.2014.00662>
- Visser, M. M., Heijenbrok-Kal, M. H., Spijker, A. V., Oostra, K. M., Busschbach, J. J., & Ribbers, G. M. (2015). Coping, problem solving, depression, and health-related quality of life in patients

References

- receiving outpatient stroke rehabilitation. *Archives of Physical Medicine and Rehabilitation*, 96(8), 1492–1498. <https://doi.org/10.1016/j.apmr.2015.04.007>
- Wade, D. T., & Hewer, R. L. (1987). Functional abilities after stroke: Measurement, natural history and prognosis. *Journal of Neurology Neurosurgery and Psychiatry*, 50(2), 177–182. <https://doi.org/10.1136/jnnp.50.2.177>
- Wade, D. T., Langton-Hewer, R., Wood, V. A., Skilbeck, C. E., & Ismail, H. M. (1983). The hemiplegic arm after stroke: measurement and recovery. *Journal of Neurology, Neurosurgery, and Psychiatry*, 46(6), 521–524.
- Wager, T. D., & Atlas, L. Y. (2015). The neuroscience of placebo effects: Connecting context, learning and health. *Nature Reviews Neuroscience*, 16(7), 403–418. <https://doi.org/10.1038/nrn3976>
- Wagner, J. M., Rhodes, J. A., & Patten, C. (2008). Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. *Physical Therapy*, 88(5), 652–663. <https://doi.org/10.2522/ptj.20070255>
- Wan, C. Y., & Schlaug, G. (2010). Music making as a tool for promoting brain plasticity across the life span. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, 16(5), 566–577. <https://doi.org/10.1177/1073858410377805>
- Wang, P. P., Badley, E. M., & Gignac, M. (2006). Exploring the role of contextual factors in disability models. *Disability and Rehabilitation*, 28(2), 135–140. <https://doi.org/10.1080/09638280500167761>
- Ward, N. S., Brown, M. M., Thompson, A. J., & Frackowiak, R. S. J. (2003a). Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*, 126(11), 2476–2496. <https://doi.org/10.1093/brain/awg245>
- Ward, N. S., Brown, M. M., Thompson, A. J., & Frackowiak, R. S. J. (2003b). Neural correlates of outcome after stroke: A cross-sectional fMRI study. *Brain*, 126(6), 1430–1448. <https://doi.org/10.1093/brain/awg145>
- Wassermann, E. M., McShane, L. M., Hallett, M., & Cohen, L. G. (1992). Noninvasive mapping of muscle representations in human motor cortex. *Electroencephalography and Clinical Neurophysiology*, 85(1), 1–8. [https://doi.org/10.1016/0168-5597\(92\)90094-R](https://doi.org/10.1016/0168-5597(92)90094-R)
- Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, 54(6), 1063–1070. <https://doi.org/10.1037/0022-3514.54.6.1063>
- Wattchow, K. A., McDonnell, M. N., & Hillier, S. L. (2018). Rehabilitation Interventions for Upper Limb Function in the First Four Weeks Following Stroke: A Systematic Review and Meta-Analysis of the Evidence. *Archives of Physical Medicine and Rehabilitation*, 99(2), 367–382. <https://doi.org/10.1016/j.apmr.2017.06.014>
- Wechsler, D. (1944). *The measurement of adult intelligence (3rd ed.)*. *Psychological Science* (Vol. 258). Baltimore (MD): Williams & Wilkins. <https://doi.org/10.1037/11329-000>
- Werring, D. J., Toosy, A. T., Clark, C. A., Parker, G. J., Barker, G. J., Miller, D. H., & Thompson, A. J. (2000). Diffusion tensor imaging can detect and quantify corticospinal tract degeneration after stroke. *Journal of Neurology Neurosurgery and Psychiatry*, 69, 269–272.
- Whitall, J., Waller, S. M. C., Silver, K. H. C., & Macko, R. F. (2000). Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke*, 31(10), 2390–2395. <https://doi.org/10.1161/01.STR.31.10.2390>
- White, J. H., Bartley, E., Janssen, H., Jordan, L. A., & Spratt, N. (2015). Exploring stroke survivor experience of participation in an enriched environment: A qualitative study. *Disability and Rehabilitation*, 37(7), 593–600. <https://doi.org/10.3109/09638288.2014.935876>

References

- Whiteneck, G., & Dijkers, M. P. (2009). Difficult to Measure Constructs: Conceptual and Methodological Issues Concerning Participation and Environmental Factors. *Archives of Physical Medicine and Rehabilitation*, *90*(11 SUPPL. 1), S22-35. <https://doi.org/10.1016/j.apmr.2009.06.009>
- Wilkinson, L., Steel, A., Mooshagian, E., Zimmermann, T., Keisler, A., Lewis, J. D., & Wassermann, E. M. (2015). Online feedback enhances early consolidation of motor sequence learning and reverses recall deficit from transcranial stimulation of motor cortex. *Cortex*, *71*, 134–147. <https://doi.org/10.1016/j.cortex.2015.06.012>
- Willer, C., Ramsay, S. C., Wise, R. J. S., Friston, K. J., & Frackowiak, R. S. J. (1993). Individual patterns of functional reorganization in the human cerebral cortex after capsular infraction. *Annals of Neurology*, *33*(2), 181–189. <https://doi.org/10.1002/ana.410330208>
- Williams, L. S., Weinberger, M., Harris, L. E., Clark, D. O., & Biller, J. (1999). Development of a stroke-specific quality of life scale. *Stroke*, *30*(7), 1362–1369. <https://doi.org/10.1161/01.STR.30.7.1362>
- Willingham, D. B. (2001). Becoming aware of motor skill. *Trends in Cognitive Sciences*, *5*(5), 181–182. [https://doi.org/10.1016/S1364-6613\(00\)01652-1](https://doi.org/10.1016/S1364-6613(00)01652-1)
- Wilson, B. A., Greenfield, E., Clare, L., Baddeley, A. D., Cockburn, J., Watson, P., ... Crawford, J. (2008). *The Rivermead Behavioural Memory Test - Third Edition (RBMT-III)*. Pearson.
- Wilson, S. A., Thickbroom, G. W., & Mastaglia, F. L. (1993). Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. *Journal of the Neurological Sciences*, *118*(2), 134–144. [https://doi.org/10.1016/0022-510X\(93\)90102-5](https://doi.org/10.1016/0022-510X(93)90102-5)
- Winger, S. R., & Pargman, D. (2003). Assessment of factors associated with exercise enjoyment. *Journal of Music Therapy*, *40*(1), 57–73. <https://doi.org/10.1093/jmt/40.1.57>
- Winstein, C. J., Rose, D. K., Tan, S. M., Lewthwaite, R., Chui, H. C., & Azen, S. P. (2004). A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: A pilot study of immediate and long-term outcomes. *Archives of Physical Medicine and Rehabilitation*, *85*(4), 620–628. <https://doi.org/10.1016/j.apmr.2003.06.027>
- Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., ... Zorowitz, R. D. (2016). Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*, *47*(6), e98–e169. <https://doi.org/10.1161/STR.0000000000000098>
- Winters, C., Van Wegen, E. E. H., Daffertshofer, A., & Kwakkel, G. (2015). Generalizability of the Proportional Recovery Model for the Upper Extremity After an Ischemic Stroke. *Neurorehabilitation and Neural Repair*, *29*(7), 614–622. <https://doi.org/10.1177/1545968314562115>
- Wiseman, S., Marlborough, F., Doubal, F., Webb, D. J., & Wardlaw, J. (2014). Blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-lacunar stroke and non-stroke: Systematic review and meta-analysis. *Cerebrovascular Diseases*, *37*(1), 64–75. <https://doi.org/10.1159/000356789>
- Wolf, S. L., Winstein, C. J., Miller, J. P., Thompson, P. A., Taub, E., Uswatte, G., ... Clark, P. C. (2008). Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. *The Lancet Neurology*, *7*(1), 33–40. [https://doi.org/10.1016/S1474-4422\(07\)70294-6](https://doi.org/10.1016/S1474-4422(07)70294-6)
- Wong, K. S., Caplan, L. R., & Kim, J. S. (2016). Stroke Mechanisms. *Frontiers of Neurology and Neuroscience*, *40*, 58–71. <https://doi.org/10.1159/000448302>
- World Health Organization. (2001). *International Classification of Functioning, Disability and*

References

- Health: ICF. World Health Organization. Geneva: World Health Organization.* <https://doi.org/10.1097/01.pep.0000245823.21888.71>
- World Health Organization Quality of Life Group. (1998). World Health Organization Quality of Life Assessment (WHOQOL): Development and general psychometric properties. *Social Science and Medicine*, 46(12), 1569–1585. [https://doi.org/10.1016/S0277-9536\(98\)00009-4](https://doi.org/10.1016/S0277-9536(98)00009-4)
- Wressle, E., Eeg-Olofsson, A. M., Marcusson, J., & Henriksson, C. (2002). Improved client participation in the rehabilitation process using a client-centred goal formulation structure. *Journal of Rehabilitation Medicine*, 34(1), 5–11. <https://doi.org/10.1080/165019702317242640>
- Wright, A., Hannon, J., Hegedus, E. J., & Kavchak, A. E. (2012). Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). *Journal of Manual & Manipulative Therapy*, 20(3), 160–166. <https://doi.org/10.1179/2042618612Y.0000000001>
- Wulf, G., & Lewthwaite, R. (2009). Conceptions of ability affect motor learning. *Journal of Motor Behavior*, 41(5), 461–467. <https://doi.org/10.3200/35-08-083>
- Wulf, G., & Lewthwaite, R. (2016). Optimizing performance through intrinsic motivation and attention for learning: The OPTIMAL theory of motor learning. *Psychonomic Bulletin & Review*, 23(5), 1382–1414. <https://doi.org/10.3758/s13423-015-0999-9>
- Wulf, G., McNevin, N., & Shea, C. H. (2001). The automaticity of complex motor skill learning as a function of attentional focus. *The Quarterly Journal of Experimental Psychology*, 54(4), 1143–1154. <https://doi.org/10.1080/713756012>
- Wulf, G., & Prinz, W. (2001). Directing attention to movement effects enhances learning: A review. *Psychonomic Bulletin & Review*, 8(4), 648–660. <https://doi.org/10.3758/BF03196201>
- Yu, C., Zhu, C., Zhang, Y., Chen, H., Qin, W., Wang, M., & Li, K. (2009). A longitudinal diffusion tensor imaging study on Wallerian degeneration of corticospinal tract after motor pathway stroke. *NeuroImage*, 47(2), 451–458. <https://doi.org/10.1016/j.neuroimage.2009.04.066>
- Zatorre, R. J. (2003). Music and the Brain. *Annals of the New York Academy of Sciences*, 999, 4–14. <https://doi.org/10.1196/annals.1284.001>
- Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain plays music: auditory-motor interactions in music perception and production. *Nature Reviews Neuroscience*, 8(7), 547–558. <https://doi.org/10.1038/nrn2152>
- Zatorre, R. J., & Salimpoor, V. N. (2013). From perception to pleasure: Music and its neural substrates. *Proceedings of the National Academy of Sciences*, 110(Supplement_2), 10430–10437. <https://doi.org/10.1073/pnas.1301228110>
- Zeiler, S. R., & Krakauer, J. W. (2013). The interaction between training and plasticity in the poststroke brain. *Current Opinion in Neurology*, 26(6), 609–616. <https://doi.org/10.1097/WCO.0000000000000025>
- Zhao, Z., Wang, X., Fan, M., Yin, D., Sun, L., Jia, J., ... Gong, J. (2016). Altered effective connectivity of the primary motor cortex in stroke: A resting-state fMRI study with granger causality analysis. *PLoS ONE*, 11(11), e0166210. <https://doi.org/10.1371/journal.pone.0166210>
- Zimmerman, E., & Lahav, A. (2012). The multisensory brain and its ability to learn music. *Annals of the New York Academy of Sciences*, 1252(1), 179–184. <https://doi.org/10.1111/j.1749-6632.2012.06455.x>
- Zondervan, D. K., Friedman, N., Chang, E., Zhao, X., Augsburger, R., Reinkensmeyer, D. J., & Cramer, S. C. (2016). Home-based hand rehabilitation after chronic stroke: Randomized, controlled single-blind trial comparing the MusicGlove with a conventional exercise program. *Journal*

References

of Rehabilitation Research and Development, 53(4), 457-472.
<https://doi.org/10.1682/JRRD.2015.04.0057>

Appendix

Appendix

Description of treatments

Music-supported Therapy

Sessions: 20 individual 30-min sessions distributed in four weeks. Daily sessions from Monday to Friday.

Keyboard exercises: For this part of the training, eight consecutive notes (C. D. E. F. G. A. B. C') from a digital keyboard (CTK-810/WK110, Casio Europe GmbH, Norderstedt, Germany) were used. The keys were labeled with numbers from 1 to 8, which served as a cue to instruct participants. The exercises with the keyboard involved movements of flexion, extension, adduction and abduction of the fingers and were organized following this rationale:

- Ascendant or descendent sequences with one finger involving adjacent tones.
- Simple ascendant or descendent sequences with one finger involving non-adjacent tones.
- Complex ascendant or descendent sequences with one finger involving non-adjacent tones.
- Ascendant or descendent sequences with two neighbor fingers involving adjacent notes.
- Simple ascendant or descendent sequences with two neighbor fingers involving non-adjacent notes.
- Complex ascendant or descendent sequences with two neighbor fingers involving non-adjacent notes.
- Ascendant or descendent sequences with three/four/five neighbor fingers involving adjacent notes.
- Simple ascendant or descendent sequences with three/four/five neighbor fingers involving non-adjacent notes.
- Complex ascendant or descendent sequences with three/four/five neighbor fingers involving non-adjacent notes.
- Playing folk songs with neighbor fingers.
- Simple ascendant or descendent sequences with fingers that are not neighbors involving non-adjacent notes.

Appendix

- Complex ascendant or descendent sequences with fingers that are not neighbors involving non-adjacent notes.
- Playing folk songs with fingers that are not neighbors.

Electronic drums exercises: An electronic drum set of 8 pads (Roland drum system. TD-6KW, Roland Corporation, Hamamatsu, Japan) that produced piano sounds (C, D, E, F, G, A, B, C') was used. The pads were labeled with numbers to facilitate the production of sequences. The drum training aimed to enhance gross motor function and required movements of flexion, adduction and abduction of the shoulder as well as its internal and external rotation. Movements of flexion and extension of the elbow and wrist were needed to hit the pads. The rationale of exercises was similar to the keyboard but in this case involved the whole hand. The participant played ascendant or descendent simple and complex sequences that involved adjacent or non-adjacent tones as well as folk songs.

Conventional Therapy

Sessions: 20 individual 30-min sessions distributed in four weeks. Daily sessions from Monday to Friday.

Stretching exercises:

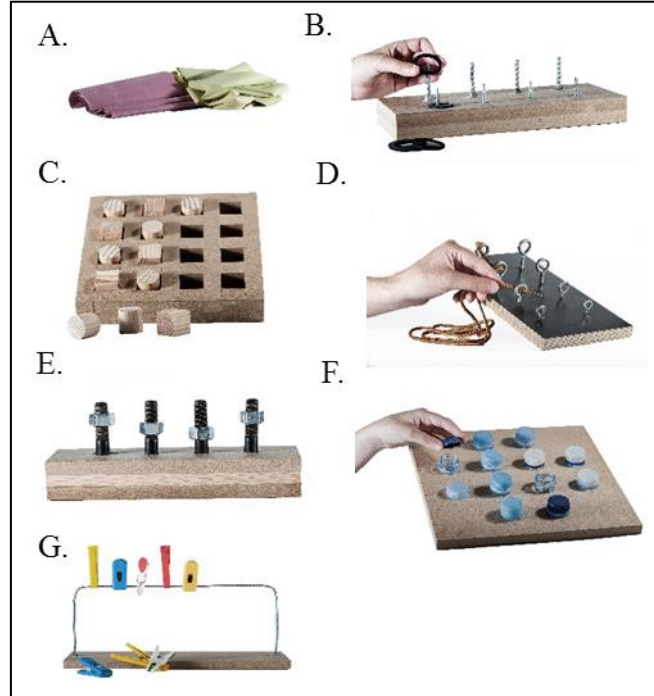
- A. Resistive exercise band wrapped on each hand with palm open to perform the following exercises with the affected extremity: thumb and finger abduction and extension, wrist extension, forearm supination, elbow extension, shoulder external rotation and abduction.

Dexterity exercises:

- B. Wooden board with screws of different heights. The participant is asked to place plastic washers over the screws and then remove them.
- C. Wooden board with eyebolts of different sizes. The participant is asked to pass a rope through the holes of the eyebolts.
- D. Wooden board with holes of 2.7 x 2.7 cm and blocks of wood (2.5 x 2.5 cm) and cylinders (1.25 cm diameter). The participant is asked to place the blocks and cylinders into the holes.
- E. Wooden board with bottle lids. The participant is asked to rotate the bottle lids.
- F. Wooden board with screws. Participant is asked to twist the nuts onto the screws.

Appendix

- G. Wooden board with a metal rod. Participant is asked to pinch clothes pins and place them on the metal.



Appendix

Description of measurements

Neurological and functional evaluations

Measure	Acronym	Domain assessed	Definition	Scoring
National Institutes of Health Stroke Scale	NIHSS	Body functions Neurological deficit (impairment)	Measures the presence and severity of symptoms associated with stroke. It is composed of 11 items assessing level of consciousness, ability to respond to simple commands, deviation of gaze, hemianopsia, hemiparesis of the face and extremities, ataxia, sensory loss, aphasia, dysarthria, and visual neglect. Each item is graded on a 3- or 4- ordinal scale, where 0 means no deficit.	0 – 42
Modified Rankin scale	mRS	Activity (limitation)	It categorises the degree of dependence in activities of daily living. The scale uses a single-item rating scale from 0 meaning no symptoms to 5 meaning severe disability.	0 – 5
Medical Research Council Scale for Muscle Strength	MRCS	Motor function (impairment)	It categorises muscle strength from 0 corresponding to complete paralysis and no palpable muscle contraction to 5 meaning normal strength with full active range of motion and normal muscle resistance.	0 – 5
Barthel Index		Activities of daily living (limitation)	It evaluates the performance in activities of daily living. It uses 10 items for activities and mobility and each item is rated taking into account is the patient is unable to perform the activity or can do it independently.	0 – 100

Appendix

Motor function tests

Measure	Acronym	Domain assessed	Definition	Scoring
Action Research Arm Test	ARAT	Activity Upper extremity function (limitation)	This test has four subtests: grasp, grip, pinch and gross movement, which are composed of different items. In each item, the patient is asked to perform a functional movement, sometimes in interaction with objects. For each item, a score between 0 (movement is not possible) and 3 (successful task accomplishment) is given assessing the quality of movement execution.	0 - 57
Arm Paresis Score	APS	Activity Upper extremity function (limitation)	Patients are asked to perform 7 functional tasks with either the affected hand or both hands. Each item is graded 0 if the patient cannot complete the task or 1 for successful task accomplishment.	0 - 7
Box and Blocks Test	BBT	Motor function (limitation)	Patients have to move as many small cubes (2.5 cm x 2.5 cm) placed in one compartment of a box to a second compartment within 1 minute as fast as they can.	Number of cubes per minute
Nine Hole Pegboard Test	9HPT	Motor function (limitation)	Patients are asked to place 9 rods (32 mm long, 9 mm diameter) into holes of 10 mm diameter as fast as they can.	Time to complete task
Fugl-Meyer Assessment of Motor Recovery after Stroke - upper extremity subtest	FMA	Motor function (impairment)	Measures reflex activity, flexor and extensor synergies of the shoulder, elbow and forearm, movements of the wrist and hand, and overall coordination and speed of the upper extremity. It has 33 items that are scored between 0 and 2.	0 - 66
Grip strength		Motor function (impairment)	Grip strength is measured with a dynamometer as the mean of three trials.	Kg
Chedoke Arm and Hand Activity Inventory	CAHAI	Activities of daily living Upper extremity function (limitation)	Measures the patients' ability in performing daily activities with both upper extremities. It consists of 13 functional tasks to complete that are scored between 1 and 7. The scoring takes into account if the patient can perform the task securely, needs physical help and which is the amount of involvement and integration of the affected upper extremity.	13 - 91

Appendix

Three-dimensional (3D) movement analysis measures

Measure	Domain assessed	Definition	Scoring
Frequency - Hand / finger tapping task	Motor function (impairment)	Number of tappings per second.	Hz
Mean velocity - Hand / finger tapping task	Motor function (impairment)	Mean velocity during the task.	mm/s
Smoothness - Hand / finger tapping task	Motor function (impairment)	Number of inversions in the velocity per movement segment.	Cycles per movement
Time to peak velocity - target task	Motor function (impairment)	Time to peak velocity in reaching the target.	ms
Maximum acceleration - target task	Motor function (impairment)	Maximum acceleration in reaching the target.	mm/s ²
Smoothness - target task	Motor function (impairment)	Number of inversions in the velocity of movements around the target in pointing.	Cycles per movement

Appendix

Cognitive function tests

Measure	Acronym	Domain assessed	Definition	Scoring
Mini-Mental State Examination	MMSE	Cognitive impairment	30-point questionnaire that evaluates orientation to time and space, registration of words, attention and calculation, recall of words, language and ability to follow instructions and visual construction.	0 - 30
Digit Span subtest Wechsler Adult Intelligence Scale III		Short-term memory and attention	The patient is asked to repeat in correct order sequences of numbers. Series increase in the number of items as the patient successfully recalls them. In this thesis, only the forward part was used.	Normative data corrected by age and level of education
Stroop Task		Response inhibition	The patient is asked to name the font color of a printed color word when there is a mismatch between ink color and word.	Normative data corrected by age
Trail Making Test		Processing speed and mental flexibility	The patient is asked to connect a set of 25 dots labeled with numbers as quickly as possible in the correct order. These dots are distributed randomly in a sheet in a way that the task requires visual search and scanning. In this thesis, only the part A of the test was used.	Time to complete the task
Rey Auditory Verbal Learning Test	RAVLT	Verbal memory	The patient is presented with a list of 15 words that has to recall. The list is repeated 5 times and the sum of the correct responses among the 5 trials is accounted as the learning score. Then, a second list of 15 words is presented and after this interference, the patient is asked to recall the first list of 15 words, which is the immediate recall part. 20 minutes later, the patient is asked to recall again the first list, which is the differed recall. Then, a list of words is presented and the patient has to tell if these words were presented in the first list or not.	Number of words correctly recalled
Rivermead Behavioral Memory Test - Story recall subtest		Verbal memory	A short story is read to the patient, who has to recall the story immediately and after a short delay with interference.	Number of correct items recalled

Appendix

Mood and quality of life tests

Measure	Acronym	Domain assessed	Definition	Scoring
Profile of Mood States	POMS	Mood	It evaluates transient and distinct mood states. The patient is asked to rate different mood states experienced during the last week from 0 (not at all) to 4 (extremely). The test is composed by six factors: Tension or Anxiety, Depression or Dejection, Anger or Hostility, Vigor or Activity, Fatigue or Inertia, and Confusion or Bewilderment.	The score of items belonging to the same factors are added.
Beck Depression Inventory Scale		Mood - depression	It measures severity of depression by asking 21 questions of multiple-choice with items related to symptoms of depression such as hopelessness and irritability, guilt, feelings of being punished and physical symptoms.	0 - 63
Positive and Negative Affect Scale	PANAS	Mood	It is comprised of two 10-item scales to measure positive and negative affect. Each item is rated on a 5-point scale from 1 (not at all) to 5 (very much).	10 - 50
Apathy evaluation scale		Mood - apathy	It evaluates apathy with behavioural, cognitive and emotional indicators.	18 - 72
Stroke-specific Quality of Life Scale		Quality of life	It comprises 12 domains evaluating energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision and productivity. Each domain contains different items asking the patient the amount of help required, trouble experienced doing tasks, and the degree of agreement with statements about functioning.	49 - 245
Health survey questionnaire SF-36		Health status and health-related Quality of life	It has 36 items evaluating physical function, role limitations due to physical problems, pain, general health, vitality, social function, role limitations due to emotional problems and mental health.	Weighted sum of the questions.
Barcelona Music Reward Questionnaire	BMRQ	Sensitivity to music reward	It has 20 statements about habits and emotions experienced in musical activities that the patient is asked to rate from 1 (completely disagree) to 5 (completely agree). The test is composed of five factors: music seeking, emotion evocation, mood regulation, sensory-motor and social.	The score of items belonging to the same factors are added.

Appendix

Transcranial Magnetic Stimulation measures

Measure	Acronym	Definition	Scoring
Hot spot		The coordinates yielding the highest MEP* in the target muscle.	x,y
Resting motor threshold	RMT	The lowest stimulus intensity needed to evoke a visible MEP (>50 μ V) in 50% of 10 trials from the relaxed target muscle.	% of maximum stimulation intensity. 0 – 100%
Active motor threshold	AMT	The minimum stimulus intensity that produces a visible MEP (>200 μ V) in 50% of 10 trials during isometric contraction of the target muscle	% of maximum stimulation intensity. 0 – 100%
Cortical silent period	CSP	The interruption of voluntary muscle contraction in response to a suprathreshold TMS pulse (150% of RMT). The target muscle is preactivated at 10% of its maximum voluntary strength. The EMG typically shows a suppression of the muscle activity, which lasts between 100 and 300 ms in healthy subjects.	Time of muscle activity suppression in ms
MEPs Peak-to-peak amplitude		Mean amplitude of 5 consecutive MEPs obtained at the Hot Spot at 125% of RMT Amplitude of the MEP.	μ V
Motor map area		Number of excitable scalp points. 5 MEPs were recorded at each position of the grid at 125% of RMT. As the difference between each spot in the grid was 1 cm, each active spot (MEPs >50 μ V) was accounted as 1 cm ² of the area of the motor map.	cm ²
Motor map volume		The volume of the map was calculated dividing the sum of the amplitudes of the motor map by the area of the map.	μ V/ cm ²
Motor map center of gravity	CoG	The center of gravity (CoG) was considered as the amplitude-weighted coordinates of the map. The coordinates of the CoG, named CoG _x and CoG _y , indicate the position of the spot in the horizontal x-axis and the vertical y-axis of the grid.	x,y

*MEP, Motor-evoked potential.

Appendix

List of figures

Figures from the General introduction

Figure 1. Stroke incidence and mortality.....	27
Figure 2. Vascular territories of the brain, brainstem and cerebellum.	30
Figure 3. International Classification of Functioning, Disability and Health.....	34
Figure 4. Typical and compensatory movements for reaching and grasping.....	37
Figure 5. Large scale processes and remodelling at the neuronal level after stroke.	40
Figure 6. Reorganisation of the primary motor cortex in rhesus monkeys.....	41
Figure 7. Example of interhemispheric reorganisation.....	42
Figure 8. Electromyographic responses after cortical stimulation.	43
Figure 9. Examples of intrahemispheric reorganisation.....	44
Figure 10. The bimodal balance-recovery model.....	46
Figure 11. Adaptive and maladaptive plastic mechanisms at the network level.	48
Figure 12. Phases of stroke recovery and neural processes.....	51
Figure 13. Model of interactions between distinct crucial elements in stroke recovery.....	53
Figure 14. The OPTIMAL theory of motor learning.....	57
Figure 15. Process for developing, evaluating and implementing complex interventions.....	65
Figure 16. Continuum of increasing evidence.....	69
Figure 17. Cortical representation of hand muscles during musical training.	74
Figure 18. Audio-motor network in chronic stroke patients treated with Music-supported Therapy.....	82
Figure 19. Motor reorganisation in chronic stroke patients treated with Music-supported Therapy.....	83

Figures from Study 1

Figure 1. Location of participants' lesions.....	104
Figure 2. Results of the RMT, AMT, and CSP measures.....	111
Figure 3. Results of the MEP amplitude and area, and volume of the TMS motor mapping.	112
Figure 4. Displacement of the CoG for the cortical maps of the FDI after Music-supported Therapy.	113
Figure 5. Reorganisation of cortical motor maps.....	114

Figures from Study 2

Figure 1. Study design and participant flow.....	127
Figure 2. Results for the primary and secondary motor outcomes.....	133
Figure 3. Results for the secondary mood and QoL outcomes.	136

Appendix

Figures from Study 3

Figure 1. Motor task for the fMRI protocol.....	148
Figure 2. Lesion overlap map for all participants.	155
Figure 3. Lesion overlap with the corticospinal tract.....	156
Figure 4. Activations during a motor task for both groups before and after the intervention.....	160
Figure 5. fMRI results for the interaction between groups and evaluation time-point.	161

Figures from Study 4

Figure 1. Location of participant's lesion and study design.	171
Figure 2. Results of the clinical motor tests.	178
Figure 3. Results of the three-dimensional (3D) movement analysis.....	180
Figure 4. Results of the keyboard performance.....	182

Figures from the General discussion

Figure 1. Elements of Music-supported Therapy.....	206
--	-----

Appendix

List of tables

Tables from the General discussion

Table 1. Levels of functioning influenced by a stroke.	36
Table 2. Recovery and compensation at the different levels of functioning.	38
Table 3. Recommendations for clinical practice based on the size of treatment effect (benefit vs risk) and its certainty (levels of evidence).	60
Table 4. Recommendations of treatments for upper extremity rehabilitation in stroke.	63
Table 5. Dimensions of treatment complexity.	64
Table 6. Measurements used in stroke motor rehabilitation.	66
Table 7. Summary of studies investigating music-based interventions for the upper extremity motor rehabilitation in stroke.	78

Tables from Research Aims

Table 1. Specific aims by studies.	94
Table 2. Summary of the methodology of each study.	95

Tables from Study 1

Table 1. Clinical description of participants.	103
Table 2. Results of the clinical motor tests (Mean, SD).	108
Table 3. Results of the TMS measures (Mean/SD).	109
Table 4. Between-groups comparisons of the TMS measures.	110

Tables from Study 2

Table 1. Demographic and clinical variables for both groups at baseline.	128
Table 2. Clinical description of participants.	130
Table 3. Results for the primary and secondary motor outcomes.	132
Table 4. Results for the secondary cognitive outcomes.	134
Table 5. Results for the secondary mood outcomes.	135
Table 6. Results for the secondary QoL outcomes.	137

Tables from Study 3

Table 1. Demographic and clinical variables for both groups at baseline.	151
Table 2. Clinical description of participants.	154
Table 3. White matter damage for both groups at baseline.	157
Table 4. fMRI results for a motor task.	159

Appendix

Tables from Study 4

Table 1. Results of the clinical motor tests..... 176

Table 2. Results of the three-dimensional (3D) movement analysis 179

Tables from the General introduction

Table 1. Summary of results regarding the levels of functioning..... 194

Table 2. Available studies validating Music-supported Therapy. 208



Supervisors:
Antoni Rodríguez-Fornells
M^aEsther Duarte Oller